JANUARY 1974

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

CUK-H0127 3-6-P024-106

(6)

Abstracts: ACC 23rd Annual Scientific Session

Clinical Studies in Coronary Artery Disease

Reperfusion After Coronary Occlusion

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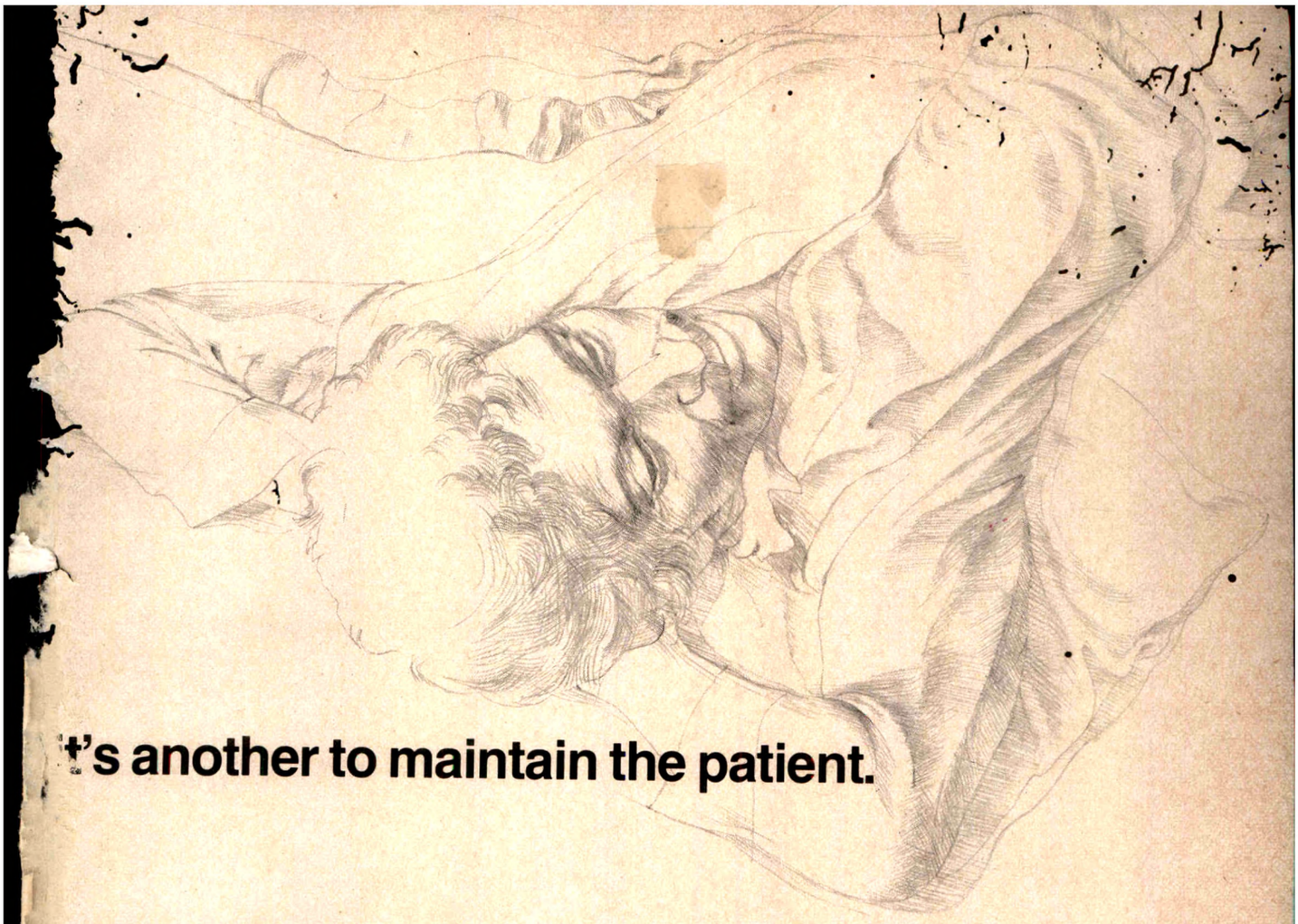
In the treatment of atrial fibrillation...

it's one thing to restore the rhythm.



t's another to maintain the patient.

How to brake the heart. The modern ethod of choice for *conversion* of atrial fibrillation normal sinus rhythm is direct current countershock. *aintaining* normal sinus rhythm—and maintaining e patient—is another matter. A "pharmacologic acemaker" that has a fundamental antiarrhythmic tion is Quinaglute® (quinidine gluconate). A specific maintaining normal sinus rhythm, Quinaglute s certain distinct advantages for long-term control:

the unique Dura-Tab® construction permits adual release of quinidine gluconate to maintain erapeutic quinidine plasma levels for 8 to 12 hours.

the convenient 8 or 12 hour dosage schedule elps avoid middle of the night dosage and early norning reversion.

Quinaglute Dura-Tabs are well tolerated with ew gastrointestinal disturbances

QUINAGLUTE® Dura-Tabs®
quinidine gluconate) 5 gr. (0.33 Gm.)
"a pharmacologic pacemaker"

Indications: For the prevention of premature atrial, nodal or ventricular contractions. For maintenance of normal sinus rhythm following conversion by other techniques of atrial, nodal or ventricular tachycardia, atrial flutter and fibrillation (paroxysmal or chronic).
Contraindications: Same as for other forms of quinidine, including partial A-V or complete heart block; intraventricular conduction defects, especially marked QRS widening; sensitivity to quinidine; renal disease with significant azotemia; development of cardiotoxic effects (conduction defects or ventricular premature beats, ventricular tachycardia, or flutter) while taking the drug; marked cardiac enlargement with congestive failure; poor renal function especially with tubular acidosis.
Precautions: Same as for quinidine. To detect idiosyncrasy, e.g., febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment, administer preliminary test dose of single tablet of quinidine sulfate. Use extreme caution in patients with severe heart disease, congestive heart failure, digitalis intoxication, renal insufficiency. Administer cautiously, if at all, to senile patients. Hospitalization (for close observation, ECG monitoring and possibly plasma quinidine levels) indicated when administering large doses with patients presenting increased risk. With the dosage regimen (see "Dosage") of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythms. Should not be used during pregnancy.
Adverse reactions: Instruct patients to report any symptoms of cinchonism at once (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, and respiratory distress); the drug should be discontinued immediately if such symptoms or evidence of hypotension occur. If gastrointestinal disturbances (rarely reported) occur, they may be minimized by administering the drug with food, or if they persist, dosage should be decreased.
Dosage: The dosage varies considerably depending upon the general condition and cardiovascular state of the patient. The quantity and frequency of administration must be determined for each patient. For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours. For maintenance of normal sinus rhythm following conversion by other techniques of atrial fibrillation, tachycardia or flutter, 2 tablets every 12 hours or 1½-2 tablets every 8 hours are usually required. The occasional patient may be maintained in normal rhythm on a dosage of 1 tablet every 12 or 8 hours. Occasionally larger or more frequent dosage may be required, but such increases should be used only after thorough evaluation of the patient, including serial electrocardiograms and determination of plasma quinidine levels. The ideal dosage is the minimum amount of total dose and frequency of daily administration that will prevent premature contractions, paroxysmal tachycardias, and maintain normal sinus rhythm.
Supplied: Bottles of 100 and 250 tablets.

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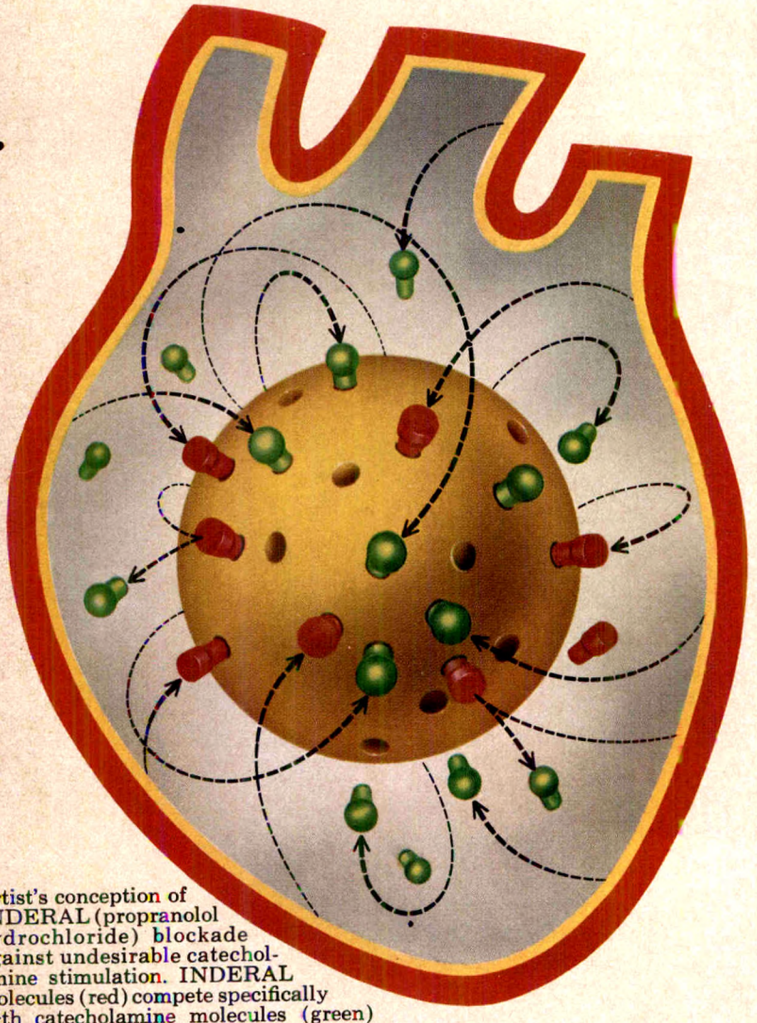
When the heart is under catecholamine siege

INDERAL®

Brand of

propranolol hydrochloride

The beta-adrenergic blocking agent for many cardiac arrhythmias



Artist's conception of INDERAL (propranolol hydrochloride) blockade against undesirable catecholamine stimulation. INDERAL molecules (red) compete specifically with catecholamine molecules (green) for available beta-receptor sites in cardiac tissue. With fewer catecholamine molecules gaining access to these sites, beta-adrenergic stimulation is reduced proportionately.

P 24,106

As the first beta-adrenergic blocking agent in clinical cardiologic use, INDERAL (propranolol hydrochloride) helps prevent or control catecholamine-induced supraventricular cardiac arrhythmias by means of a unique mechanism of action.

Excitatory adrenergic activity from sympathetic nerve endings and the adrenal medulla is mediated in myocardial and pacemaker tissue via beta receptors. Through blockade of undesirable catecholamine stimulation at these sites, INDERAL decreases impulse formation and conduction, and thus the rate and force of myocardial contraction. The clinical benefit is generally a reduction of supraventricular rate, a slowing of ventricular response, and restoration to sinus rhythm in many cases. In responsive patients, a subsequent maintenance regimen of 10 to 30 mg. INDERAL three or four times daily can prevent recurrence or reduce the frequency and severity of paroxysmal attacks.

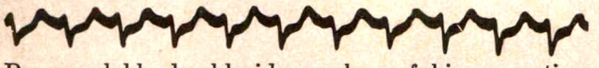
With its unique site of action, INDERAL does not interfere with the therapeutic actions of nonadrenergic cardiotonic agents. Thus INDERAL can be used in combination—or alone—to control arrhythmias when other drugs have failed to produce a satisfactory response.

INDERAL is especially effective in the management of catecholamine-induced supraventricular arrhythmias. The response of ventricular arrhythmias is generally less predictable.

INDERAL has proved to be of particular value in the control of digitalis-induced arrhythmias.

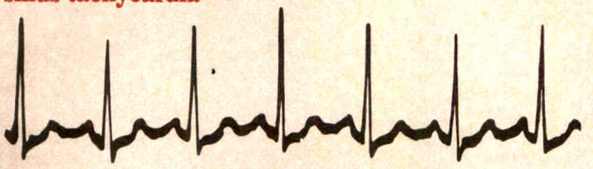
Proved effective over 6 years' clinical use

paroxysmal atrial tachycardia[1-8]



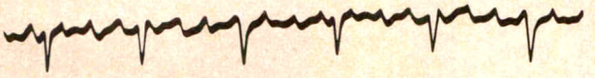
Propranolol hydrochloride may be useful in preventing recurrent attacks of paroxysmal atrial tachycardia "including attacks which may be a part of the Wolff-Parkinson-White syndrome."[1]

sinus tachycardia[9]



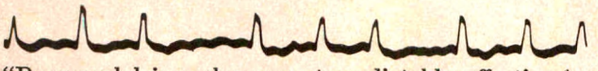
Sonnenblick "would use propranolol hydrochloride in treating a rapid sinus tachycardia which is poorly tolerated by the circulation—if the tachycardia were not due to some underlying process such as occult blood loss."[9]

atrial flutter[4-6,8-11]



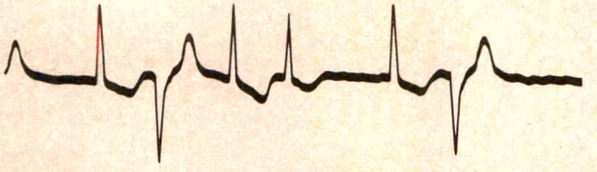
"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not being controlled by digitalis, especially in the presence of mitral valve disease."[9]

atrial fibrillation[1,3-10]



"Propranolol is perhaps most predictably effective in the treatment of patients with atrial fibrillation. It reduces the ventricular rate by prolonging the functional refractory period of the atrioventricular node. This occurs whether or not the patient is receiving digitalis."[3]

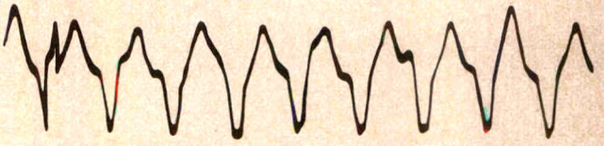
arrhythmias of digitalis intoxication[1,3-6,8-10]



"Propranolol has been especially useful in treating patients with arrhythmias in the presence of established or suspected digitalis toxicity. All too common is the clinical situation in which we know the patient has had digitalis, but do not know whether he is toxic to digitalis. Propranolol may be a very useful drug in this situation."[1]

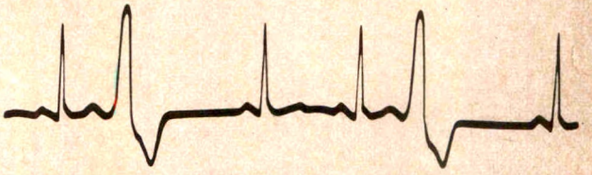
According to Wehrmacher, propranolol hydrochloride "is probably the treatment of choice for digitalis-induced tachyarrhythmias."[10]

ventricular tachycardias (when a matter of minutes in controlling the arrhythmia may mean life or death and when cardioversion technics are not available)[3,4,7,9,10,12]



"There appears to be a special place for the use of propranolol in patients with prolonged cardiac arrest associated with resistant, recurrent ventricular fibrillation. Propranolol has been shown to have an anti-fibrillatory effect, and we [the clinicians] believe it should be used when standard resuscitation methods and drugs have not produced a satisfactory cardiac rhythm."[12]

arrhythmias associated with anesthesia in selected cases[3,10,12-15]



In the treatment of cardiac disturbances occurring during and/or following halothane anesthesia for cardiovascular operations, 141 episodes in 115 patients "responded consistently to 1 to 2 mg. of propranolol intravenously without serious side effects. The onset of the drug's action was apparent within one to three minutes after its injection."[13]

Also recommended in the management of hypertrophic subaortic stenosis...[5,10,16]

Oral administration has produced symptomatic improvement in a large majority of patients, some treated for several days, and others for as long as several months.[10]

...and pheochromocytoma[3,6,8,10,17,18]

"When surgical removal [of the tumor in pheochromocytoma] is impossible, administration of both α- and β-adrenergic blocking drugs is essential for long-term control."[10]

Administered with awareness of the Contraindications, Warnings, Precautions, and Adverse Reactions, INDERAL (propranolol hydrochloride) provides a valuable tool in controlling a wide variety of cardiac arrhythmias, including cases that have proved refractory to previous therapy with other drugs.

With judicious use of INDERAL in suitably selected patients, symptomatic improvement is most frequently obtained; restoration to sinus rhythm is often possible.

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BETA-BLOCKADE / **INDERAL®**
(propranolol hydrochloride)

Ayerst®

(See last page of advertisement for prescribing information)

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL®
(propranolol hydrochloride)

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS

Cardiac Arrhythmias

1) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL (propranolol hydrochloride) should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

In chronically treated patients, dosage should be gradually reduced over a two week period when it is anticipated that the administration of INDERAL will be discontinued. There have been a few reports of myocardial infarction occurring within 2-3 days of propranolol hydrochloride discontinuation in angina pectoris patients, but an association has not yet been established.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

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INDERAL (propranolol hydrochloride)

TABLETS—No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

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THE AMERICAN JOURNAL OF CARDIOLOGY,® Official Journal of the American College of Cardiology, January, 1974, Vol 33, No. 1.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except September, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group, William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES, 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

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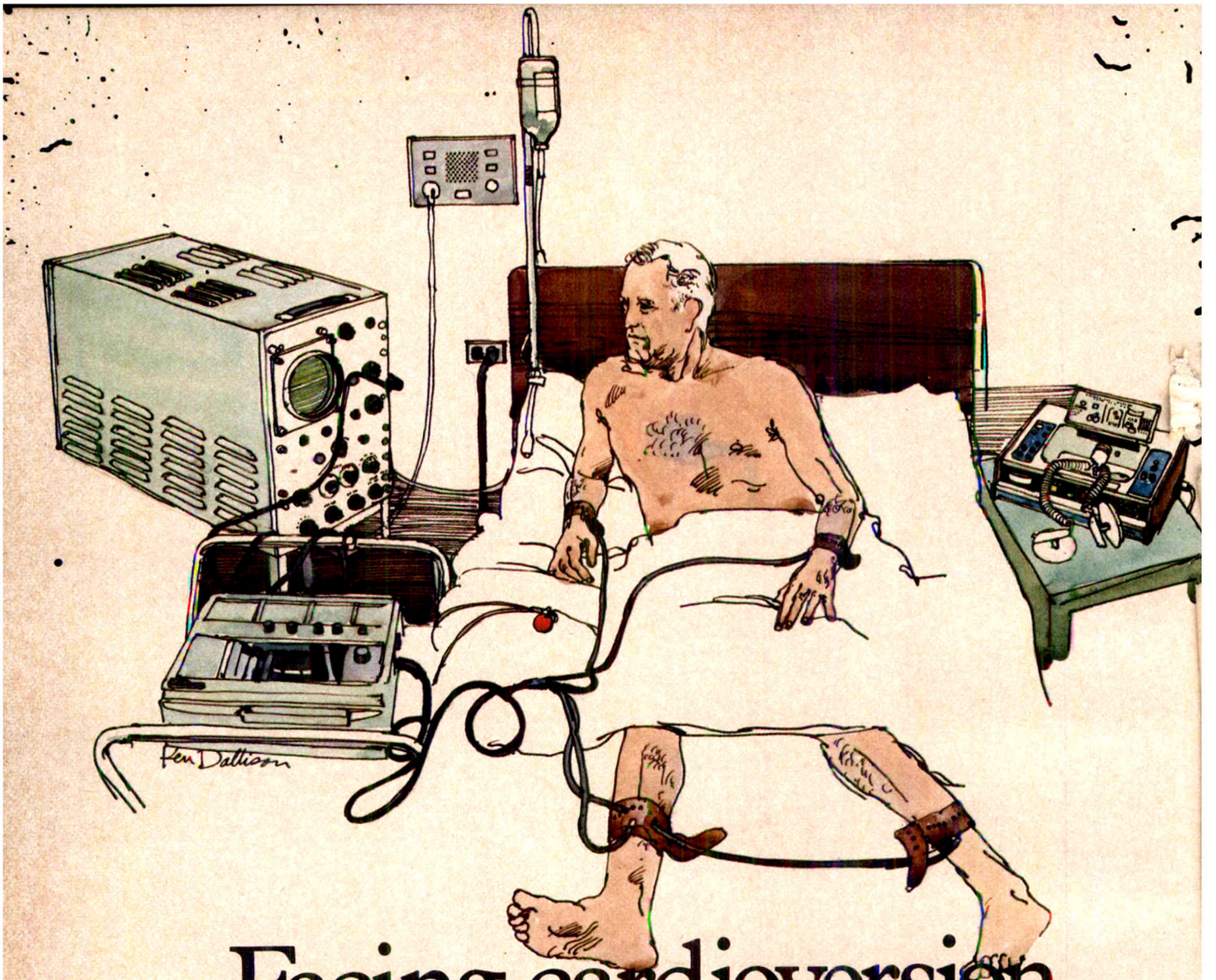

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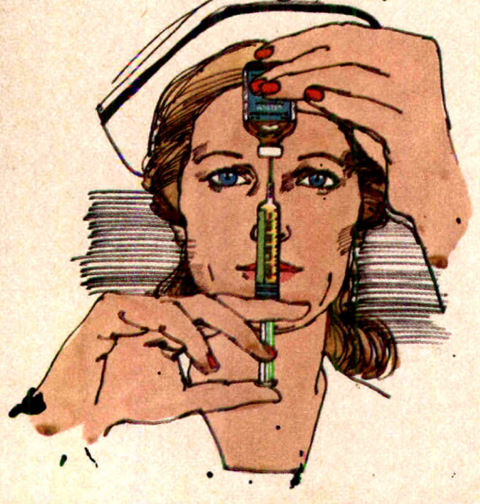

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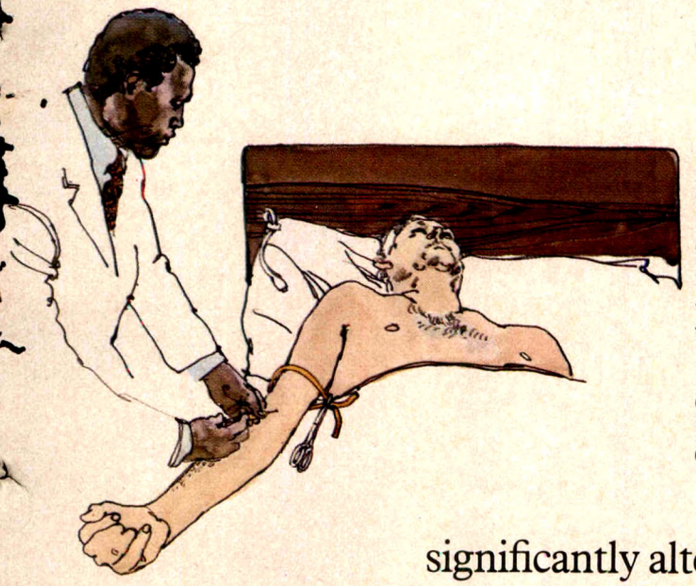

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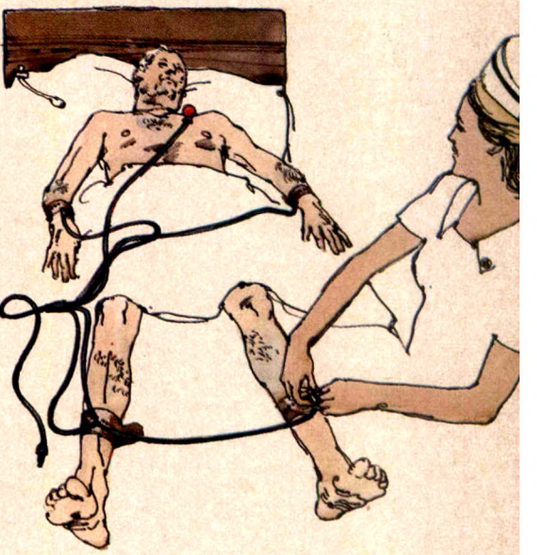

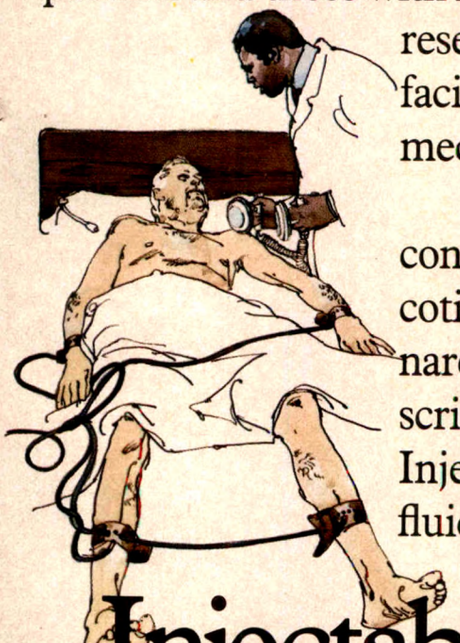

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Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis and phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.) Give I.V. injections slowly, directly into vein; take at least 1 minute for each 5 mg (1 ml); avoid small veins. I.M. should be by deep injection. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids. Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

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12 **Effects of Factors Predisposing to Atherosclerosis on Formation of Coronary Collateral Vessels.** Robert A. Heinle, Robert I. Levy and Richard Gorlin

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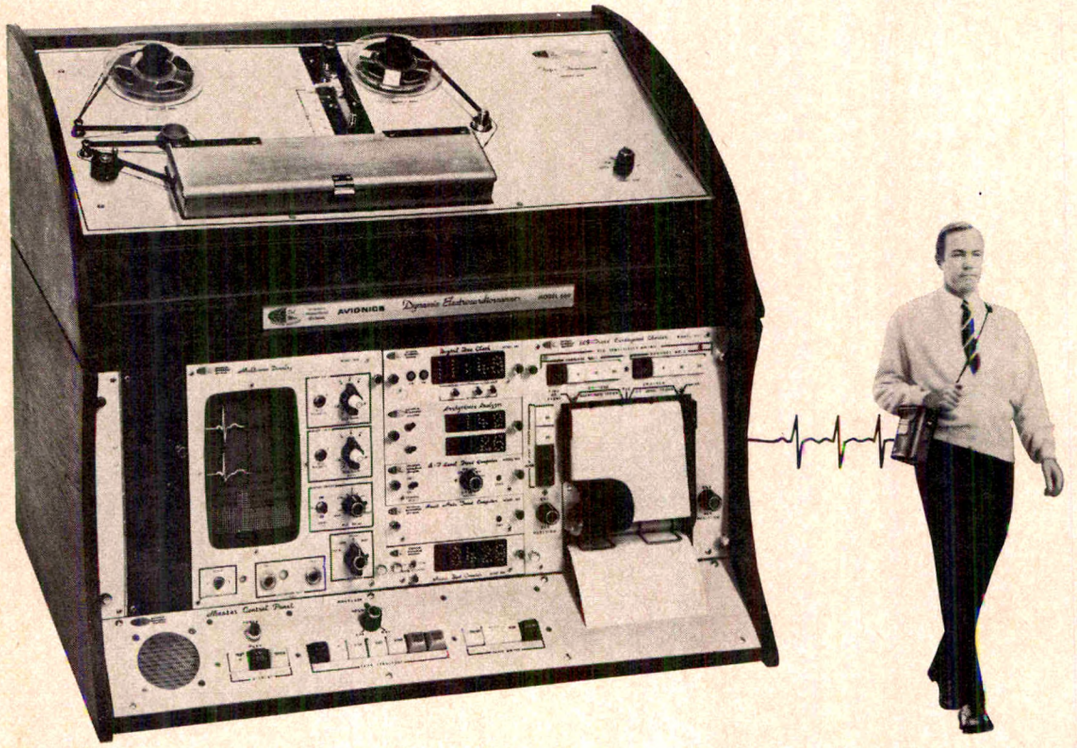

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CLINICAL STUDIES

1 **Comparison of Biplane and Single Plane Left Ventriculograms in Patients with Coronary Artery Disease**

PETER F. COHN, RICHARD GORLIN, DOUGLASS F. ADAMS, ROBERT A. CHAHINE, PANTEL S. VOKONAS and MICHAEL V. HERMAN

In biplane left cineventriculographic studies of 10 normal patients, volumetric analyses indicated good agreement between minor diameters in the right and left anterior oblique views and between ventricular volumes and ejection fractions determined by single plane and biplane techniques. In 50 patients with coronary artery disease more scatter in these values was attributed to loss of ventricular symmetry. The biplane technique allowed comprehensive evaluation of ventricular asynergy and overall function in patients with prior myocardial infarction and ventricular enlargement.

7 **Devolutionary Pattern of Coronary Atherosclerosis in Patients with Angina Pectoris. Coronary Arteriographic Studies**

DEMETRIOS KIMBIRIS, PETER LAVINE, HANS VAN DEN BROEK, MOOSA NAJMI and WILLIAM LIKOFF

As observed cinearteriographically in 47 patients, the devolutionary pattern of coronary arteriosclerosis in patients with angina pectoris is unpredictable and unrelated to the common risk factors. Severity of angina pectoris is the best guide to progressive coronary artery disease although progressive disease can occur without affecting angina. Not all determinants influencing myocardial perfusion are identified by cinearteriography.

12 **Effects of Factors Predisposing to Atherosclerosis on Formation of Coronary Collateral Vessels**

ROBERT A. HEINLE, ROBERT I. LEVY and RICHARD GORLIN

This study of 218 consecutive patients undergoing selective coronary angiography found no measurable clinical factors that permit prediction of coronary collateral channels in an individual patient. Factors predisposing to atherosclerosis have a similar distribution in patients with and without such collateral vessels.

17 **Hemodynamic Observations in Patients with Unstable Angina Pectoris**

DAVID S. CANNOM, DONALD C. HARRISON and JOHN S. SCHROEDER

Three distinctive hemodynamic responses to spontaneous angina were observed during monitoring of brachial and pulmonary arterial pressures in 26 patients with unstable angina pectoris and documented occlusive coronary artery disease. Group I had only increased heart rate, Group II had associated increases in brachial arterial pressure and slight increases in heart rate, Group III showed increased brachial and pulmonary arterial diastolic pressures and minimal change in heart rate. Such changes suggest different pathogenic mechanisms for spontaneous angina which may be specific for individual patients.

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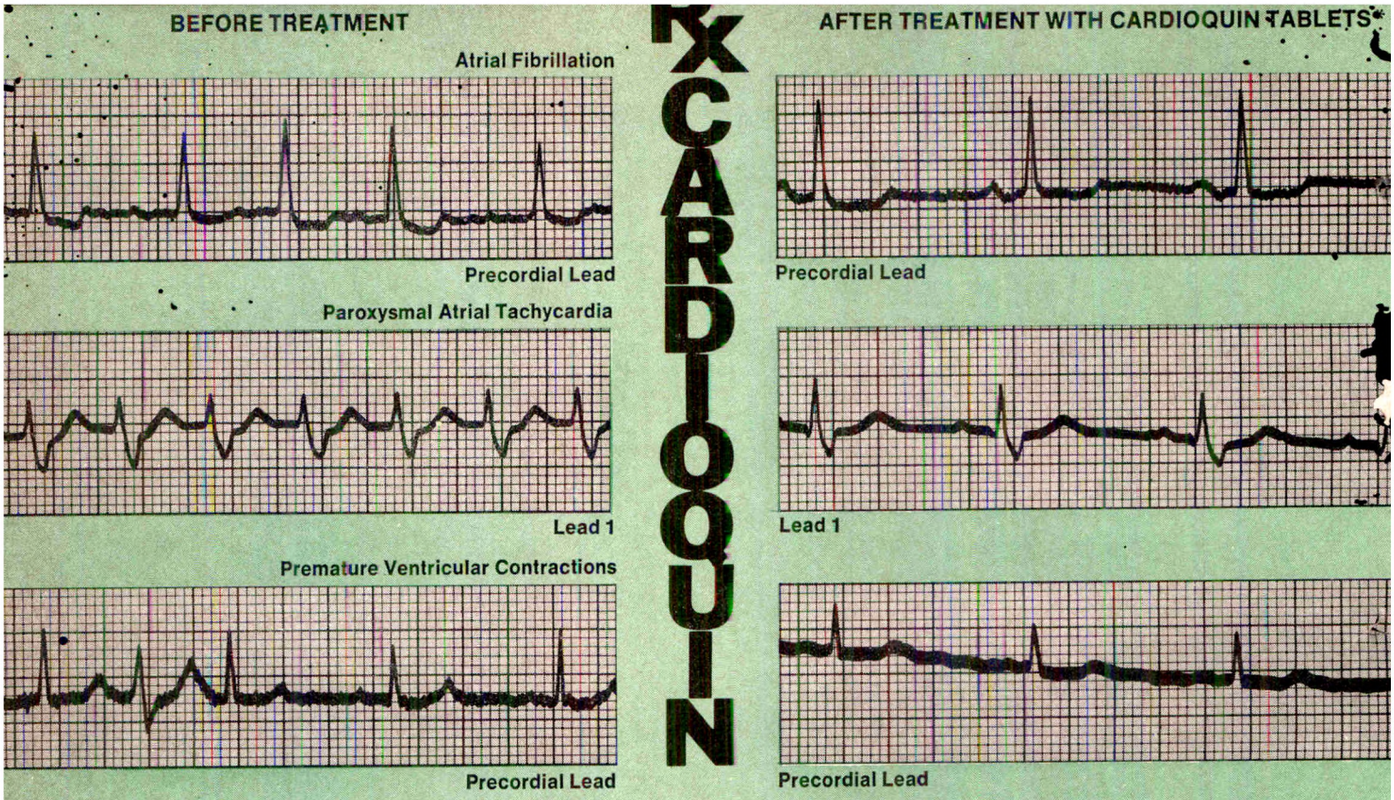

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23 **Maximal Cardiac Output During Exercise in Patients with Coronary Artery Disease**

JOHN R. McDONOUGH, RUTH A. DANIELSON, ROBERT E. WILLS and DONALD L. VINE

Measurements in 16 patients with coronary artery disease who exercised to the point of exhaustion revealed that maximal cardiac output paralleled the maximal oxygen uptake and was reflected by a plateau during the final minutes of exercise in which significantly decreased stroke volume and increased mean pulmonary arterial pressure were observed. Acute left ventricular dysfunction, rapidly reversed during the initial seconds of recovery after exercise, was the factor limiting cardiac output in these patients.

30 **Effects of Submaximal Isometric Handgrip on Left Ventricular Size and Wall Motion**

PHILIP LUDBROOK, JOEL S. KARLINER and ROBERT A. O'ROURKE

The normal response to submaximal isometric handgrip exercise at 15 percent of maximal voluntary capacity is a decrease in left ventricular size and in amplitude and velocity of left ventricular wall motion. In patients with previous myocardial infarction sustained isometric handgrip exercise proved useful to intensify or induce left ventricular wall motion abnormalities. In contrast, systolic time intervals were not useful to evaluate the left ventricular response to submaximal handgrip exercise in normal subjects or those with previous infarction.

37 **Enhanced Left Ventricular Performance with Phentolamine in Acute Myocardial Infarction**

PAUL WALINSKY, KANU CHATTERJEE, JAMES FORRESTER, WILLIAM W. PARMLEY and H. J. C. SWAN

Decreased afterload after the administration of phentolamine improved depressed left ventricular function in nine patients with acute myocardial infarction and increased left ventricular filling pressure. Similar improvement did not occur in five patients with normal left ventricular pressure.

42 **Results of Aortocoronary Artery Saphenous Vein Bypass Surgery for Ischemic Heart Disease**

MOOSA NAJMI, KIYOJI USHIYAMA, GUMERSINDO BLANCO, ALBERTO ADAM and BERNARD L. SEGAL

A 12 percent operative or early hospital mortality rate occurred in 100 consecutive patients with ischemic heart disease who had aortocoronary artery saphenous vein bypass grafts. Clinical results, as measured by angina and results of exercise stress tests, correlated best with arterial blood flow through the bypass, which was directly related to the state of the distal coronary arterial system.

EXPERIMENTAL STUDIES

49 **Closed Chest Model of Intracoronary Occlusion for Study of Regional Cardiac Function**

ELIOT CORDAY, TZU-WANG LANG, SAMUEL MEERBAUM, HERBERT GOLD, SHIGERU HIROSE, STEVEN RUBINS and MARINA DALMASTRO

This new model of experimental coronary occlusion provides the means for independent and comprehensive investigations of cardiac function in ischemic and nonischemic myocardium. Intracoronary epicardial electrocardiograms permit correlation with regional hemodynamic and metabolic events. One study using this model showed that when ventricular tachycardia occurred, the net myocardial potassium loss increased in both the occluded and nonoccluded segments of the heart to 13 percent above the preocclusion level, thereby suggesting that the nonoccluded myocardium may also be seriously affected by arrhythmias.

Continued on page A-15

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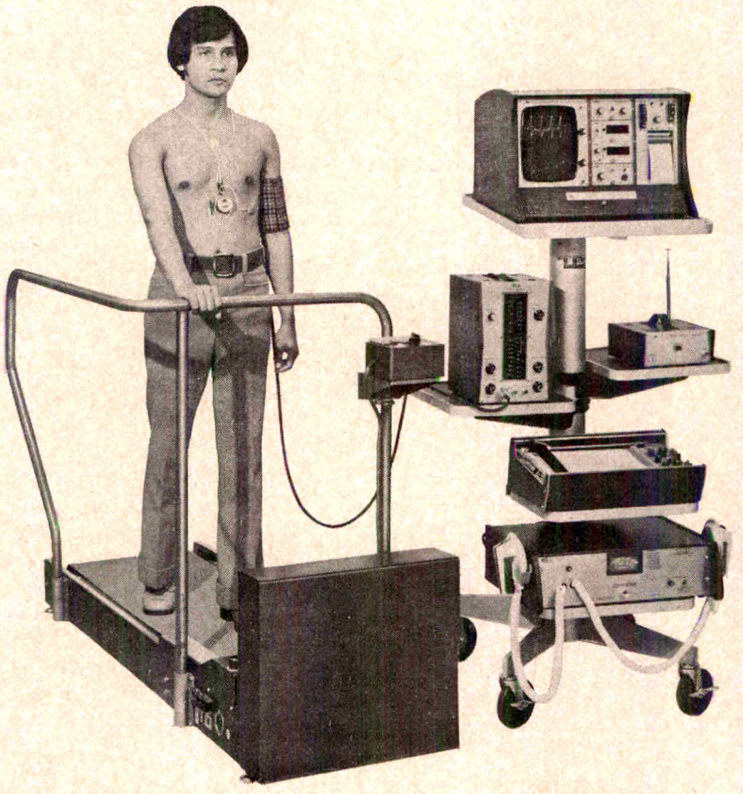

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60 Progressive Alterations of Cardiac Hemodynamic and Regional Metabolic Function After Acute Coronary Occlusion

SAMUEL MEERBAUM, TZU-WANG LANG, ELIOT CORDAY, STEVEN RUBINS, SHIGERU HIROSE, COSTANTINO COSTANTINI, HERBERT GOLD and MARINA DALMASTRO

The most striking finding in this study of 34 closed chest dogs after 3 hours of intracoronary balloon occlusion of the left anterior descending artery was the significant metabolic dysfunction, manifested by disturbed regional lactate metabolism and potassium loss, that occurred in the nonoccluded segment after the occlusion period. This change may be attributed to a decrease in regional coronary flow or to increased oxygen demands in this zone resulting from increased left ventricular overload. Individual experiments often revealed a distinct metabolic-mechanical dissociation.

69 Consequences of Reperfusion After Coronary Occlusion. Effects on Hemodynamic and Regional Myocardial Metabolic Function

TZU-WANG LANG, ELIOT CORDAY, HERBERT GOLD, SAMUEL MEERBAUM, STEVEN RUBINS, COSTANTINO COSTANTINI, SHIGERU HIROSE, JULES OSHER and VICTOR ROSEN

Reperfusion for 5 hours after 3 hours of coronary occlusion in seven closed chest dogs produced intermittent ectopic arrhythmias in five and severe shock in two dogs as well as histopathologic changes of accelerated necrosis, reactive hyperemia, hemorrhage and other apparently irreversible abnormalities. Only two animals showed persistent improvement of hemodynamic indexes. These studies indicate that serious hemodynamic, metabolic and morphologic abnormalities can occur after reperfusion.

82 Deleterious Effects Due to Hemorrhage After Myocardial Reperfusion

GERALD F. BRESNAHAN, ROBERT ROBERTS, WILLIAM E. SHELL, JOHN ROSS, Jr. and BURTON E. SOBEL

Reperfusion 5 hours after experimental coronary arterial occlusion resulted in myocardial hemorrhage and extension of myocardial infarction in 44 percent of 16 conscious dogs and was not without further hazard during evolving myocardial infarction.

87 Physiologic Basis for Assessing Critical Coronary Stenosis. Instantaneous Flow Response and Regional Distribution During Coronary Hyperemia as Measures of Coronary Flow Reserve

K. LANCE GOULD, KIRK LIPSCOMB and GLEN W. HAMILTON

Resting coronary blood flow and regional distribution are insensitive indexes for determining critical stenosis. Coronary flow responses to temporary occlusion and to selective main coronary arterial injection of sodium diatrizoate in 12 dogs demonstrated that resting coronary flow is unaltered until 85 percent of the arterial diameter is constricted, whereas maximal coronary flow is affected by constriction as small as 30 percent. Flow response and regional distribution during coronary hyperemia caused by Hypaque are valid quantitative measures for physiologically assessing critical coronary stenosis and flow reserve.

Continued on page A-17

Drug-Induced Constipation

Many of the widely prescribed drug categories—antacids, analgesics, barbiturates, tranquilizers, diuretics, hematinics, antihistamines, anticholinergics, antispasmodics, narcotics, muscle relaxants, antihypertensives, antidepressants—may interfere with the regular bowel action.

The value of SENOKOT Tablets/Granules has been clearly demonstrated in drug-induced or drug-aggravated constipation. In 5 studies* SENOKOT therapy was effective in 98.5% of 613 cases.

When an essential drug you prescribe induces or aggravates constipation, Rx or recommend a SENOKOT laxative product. Compatible with antacids, clinically tested, shown not to interfere with the action of numerous drugs, it is the *natural* choice to keep things moving gently, comfortably, effectively.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.

*References on request.

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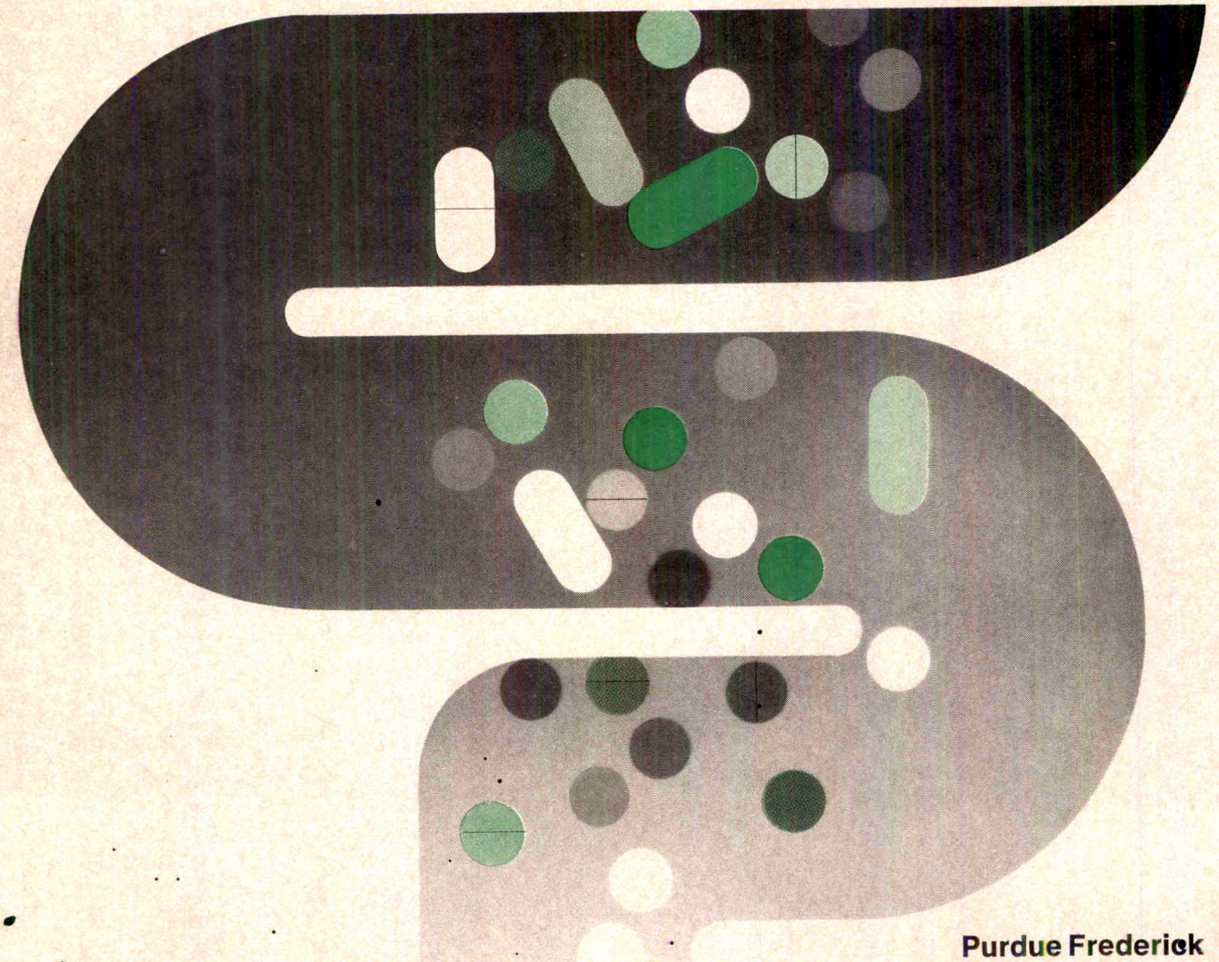
(standardized senna concentrate)
Tablets/Granules

a natural laxative



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PEDIATRIC CARDIOLOGY

95 **Cardiac Specialized Tissue in Hearts with an Apparently Single Ventricular Chamber (Double Inlet Left Ventricle)**

ROBERT H. ANDERSON, ROBERT ARNOLD, MOHINDER K. THAPAR, RICHARD S. JONES and DAVID I. HAMILTON

This investigation establishes that specialized tissue is unexpectedly situated in hearts of the "single" ventricular type. In all 14 univentricular hearts the atrioventricular node was a small hypoplastic structure in the interatrial septum. An anterior node at the junction of the right atrial appendage and the anterior interatrial septum connected the atria and ventricles. Such hearts should be distinguished from "common" ventricles in which the specialized tissue is reported to lie in the posterior position.

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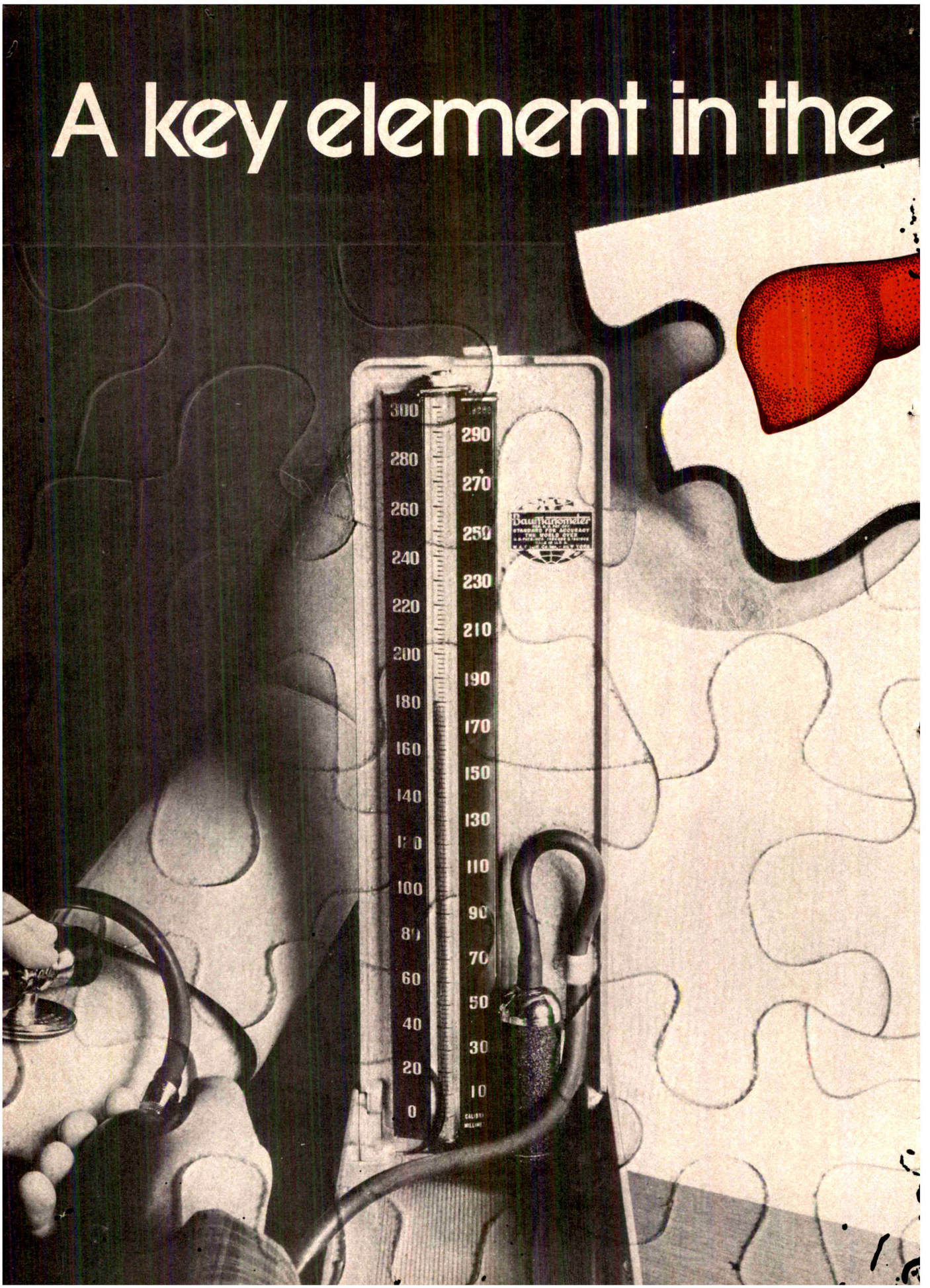
A key element in the



hypertension puzzle

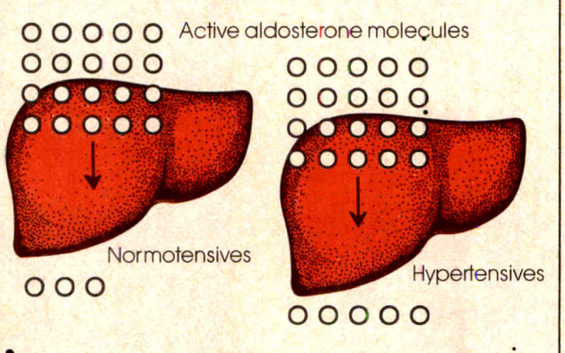
The liver metabolizes significantly less aldosterone in hypertensives than in normotensives.[1,2]

A significantly decreased hepatic MCR (metabolic clearance rate) of aldosterone, without significantly decreased SR (secretion rate), was demonstrated in approximately 90 percent of a group of 56 patients with benign essential hypertension.[1]

Thus "Failure of the aldosterone SR to fully adapt to the decrease in MCR may be responsible for a relative state of hyperaldosteronism in many patients with BEH [benign essential hypertension], even when the secretion and excretion rates are within normal range.

"It is conceivable that it is the mineralocorticoid [aldosterone] excess that is leading to an increase of sodium content in the arteriolar wall and the hypertensive process itself, in many patients with BEH."[2]

Metabolic clearance of aldosterone in hypertensives and in normotensives*



*Schematic representation

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

- Spironolactone blocks the pressor effect of aldosterone at the arteriole,[3-5] and exerts natriuretic action in the distal renal tubule.
- Hydrochlorothiazide exerts additive antihypertensive effect through its action at a different renal site.
- Aldactazide helps maintain potassium balance—without the need for potassium supplements—because the potassium-sparing action of spironolactone offsets the potassium-losing effect of hydrochlorothiazide.

References: 1. Genest, J., in Thorn, G. W., and Melby, J. C. (Editors): Aldosterone in Clinical Medicine, Medcom® Learning Systems, New York, Medical Communications, Inc., 1972, pp. 64-75.
2. Nowaczynski, W.; Kuchel, O., and Genest, J., in Genest, J., and Koiw, E. (Editors): Hypertension '72, Berlin, Springer-Verlag, 1972, pp. 244-255.
3. Crabbé, J.: Acta Endocrinol. (Kbh) *47*:419-432 (Nov.) 1964.
4. Liddle, G. W.: Arch. Intern. Med. *102*:998-1004 (Dec.) 1958.
5. Liddle, G. W.: Ann. N.Y. Acad. Sci. *139*:466-470 (Nov. 22) 1966.

See following page for brief summary.

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

Indications—Hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusion may benefit from Aldactazide therapy.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of the renal function. Anuria; sensitivity to thiazides or other sulfonamide-derived drugs. Probably contraindicated in acute or severe hepatic failure.

Warnings—Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Potassium supplementation is recommended only in exceptional instances, but may be considered when a glucocorticoid is also given. Utilize normal dietary sources of potassium if possible when potassium supplementation is necessary. If enteric-coated potassium is used be alert to the possible development of hemorrhagic, stenotic, ulcerated or perforated small-bowel lesions; deaths have occurred. The possibility of exacerbation or activation of systemic lupus erythematosus by sulfonamide derivatives, including thiazides, has been reported.

Administer thiazides with caution to pregnant or lactating patients. Adverse reactions which may occur in the adult (hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, etc.) may possibly occur in the newborn, since thiazides cross the placental barrier and may also appear in breast milk.

Precautions—Consider the possibility of fluid and electrolyte imbalance. Serum and urine electrolyte determinations are particularly important in patients with excessive vomiting or in those receiving fluids parenterally. Medications such as digitalis may also influence serum electrolytes. Warning signs of possible fluid and electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains, cramps or fatigue, hypotension, oliguria, tachycardia, gastrointestinal symptoms. Hypokalemia may develop with brisk diuresis in severe cirrhosis or during the concomitant use of glucocorticoids or ACTH. Inadequate oral electrolyte intake contributes to hypokalemia. Hypokalemia may cause signs of digitalis intoxication with previously tolerated doses of digitalis.

Give Aldactazide cautiously to patients with severe liver disease since thiazides can precipitate hepatic coma; discontinue if mental confusion increases. Consider also other factors that may precipitate hepatic coma, including blood in the gastrointestinal tract or preexistent potassium depletion. Reversible elevation of NPN and BUN may occur in some patients receiving Aldactazide. The most common electrolyte disturbance is dilutional hyponatremia which requires appropriate corrective measures. A true low-salt syndrome is rare; discontinue Aldactazide and administer sodium for this condition.

Although rare, the most potentially serious electrolyte disturbance is hyperkalemia; if this occurs discontinue Aldactazide and restrict potassium intake. Rarely, fatality due to hyperkalemia has been reported. Hyperkalemia is more likely to occur in severely ill patients with relatively small urine output or in patients receiving supplemental potassium; determine serum electrolytes frequently in such patients. Consider the possibility of hyperuricemia or a decrease in tolerance to glucose.

Patients with severely resistant edema may have an increased diuretic response following the addition of a potent glucocorticoid, such as 15 to 20 mg. of prednisone daily, to Aldactazide therapy. Supplemental potassium will usually be necessary in such patients and the usual precautions with glucocorticoids are necessary. Use caution if regional or general anesthesia is necessary since Aldactazide reduces vascular responsiveness to norepinephrine in such patients. Thiazides may increase responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in patients who have undergone sympathectomy.

Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may increase serum PBI levels without signs of thyroid disturbance.

Adverse Reactions reported with *spironolactone* use: Drowsiness and lethargy, mental confusion, diarrhea and other gastrointestinal symptoms, photosensitivity, mild androgenic manifestations (including hirsutism, menstrual irregularity, deepening of the voice), gynecomastia, inability to achieve or to maintain erection, headache, maculopapular or erythematous cutaneous eruptions, urticaria, drug fever, ataxia.

Adverse Reactions reported with *thiazide* use: purpura, thrombocytopenia, leukopenia, agranulocytosis, gastrointestinal disorders (anorexia, nausea, vomiting, diarrhea, abdominal cramps), rash, pruritus, paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, urticaria, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness, restlessness. Reduce dosage or withdraw drug whenever adverse reactions are moderate or severe.

Dosage and Administration—Dosage should be determined by individual titration. *For essential hypertension* the daily *adult* dosage is two to four tablets in divided doses; continue treatment for two weeks or longer. Adjust the dosage according to the response of the patient. Reduce the dosage of other antihypertensive agents, particularly ganglionic blocking agents, by 50 percent since Aldactazide potentiates the action of such drugs. *For edema, ascites or effusion in adults* the average dosage is one tablet 4 times daily; dosage may range from 1 to 8 tablets daily in divided doses. The daily dosage of Aldactazide *in children* should provide 0.75 to 1.5 mg. of Aldactone® (spironolactone) per pound of body weight.

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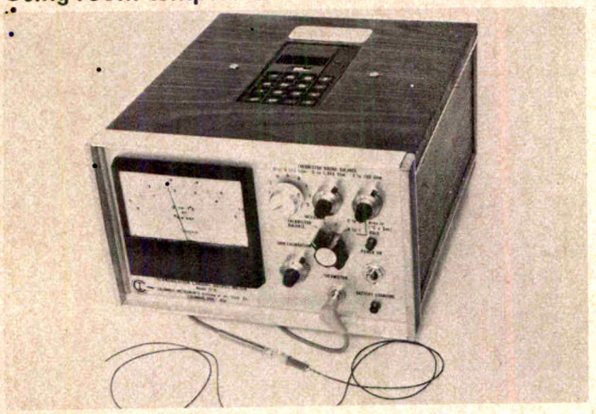

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- An intermediate instrument between the simple bridge and full scale computer.
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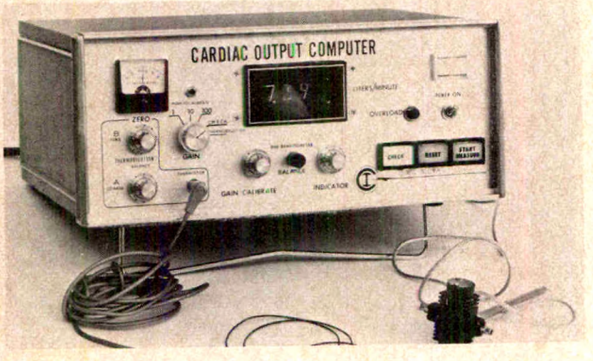

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Enduron®

METHYCLOTHIAZIDE TABLETS

ABBOTT

Brief Summary

CONTRAINDICATIONS: Anuria.
Hypersensitivity to this or other sulfonamide-derived drugs.
The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USAGE IN PREGNANCY: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS: Thiazides cross the placental barrier and appear in cord blood and breast milk.

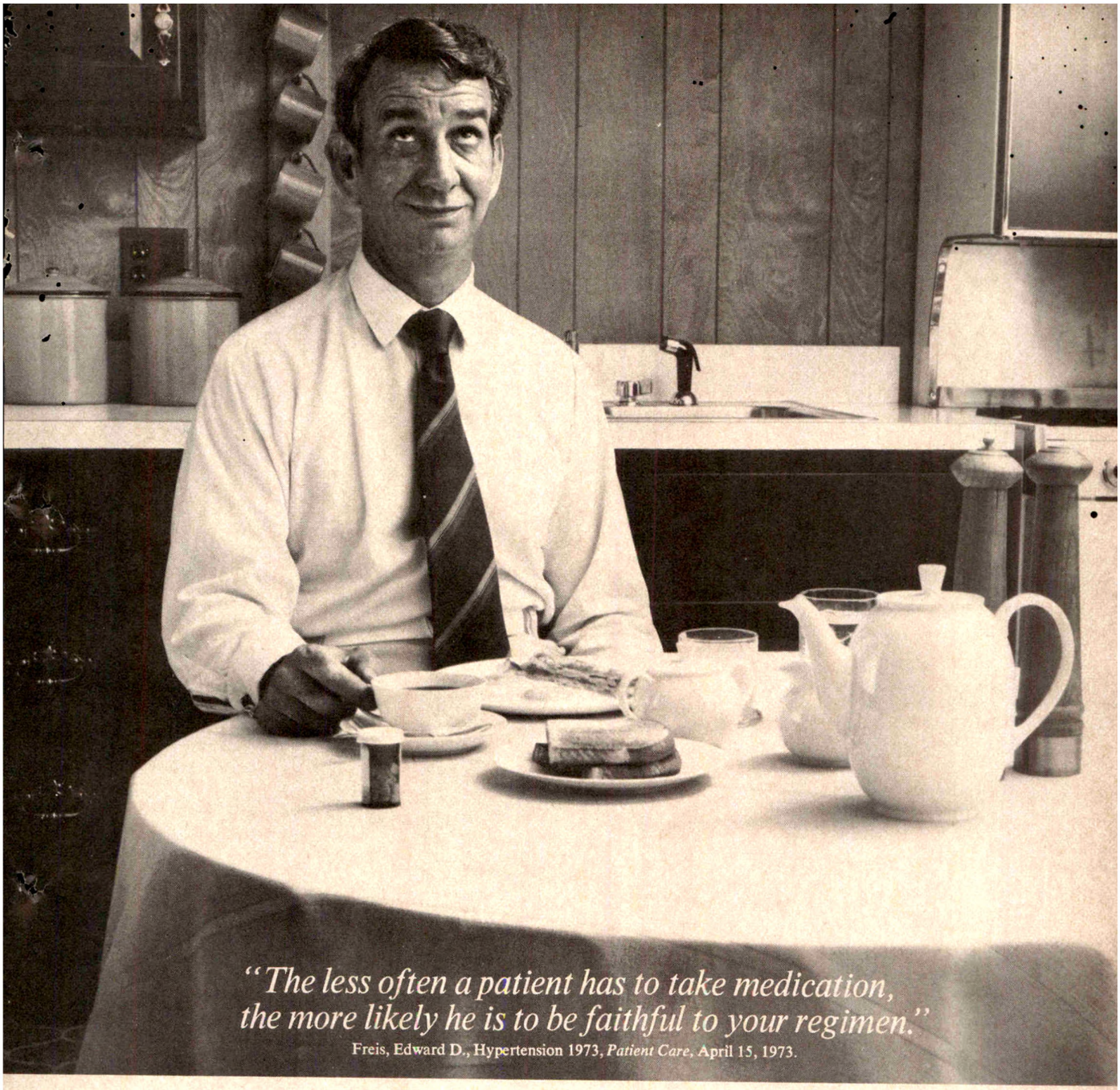
PRECAUTIONS: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: Dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.
Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening.
In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine.
The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.
Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If progressive renal impairment becomes evident as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS: Gastrointestinal system reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.
Central nervous sytem reactions: Dizziness, vertigo, paresthesias, headache, xanthopsia.
Hematologic reactions: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.
Dermatologic—hypersensitivity reactions: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis).
Cardiovascular reaction: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates, or narcotics.
Other: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

For more detailed information, consult your Abbott representative, or write:

Abbott Laboratories, Dept. 321
North Chicago, IL60064

309462



Enduron helps your hypertensive patient keep the faith.

Enduron helps your patient remain faithful to your regimen because it couldn't be simpler. Once in the morning, provides 24-hour pharmacological action . . . around the clock management of his hypertension.

A long-acting, potent diuretic . . . once a day

Enduron® 5 mg.

methyclothiazide tablets, N.F.

ABBOTT

See opposite page for Brief Summary

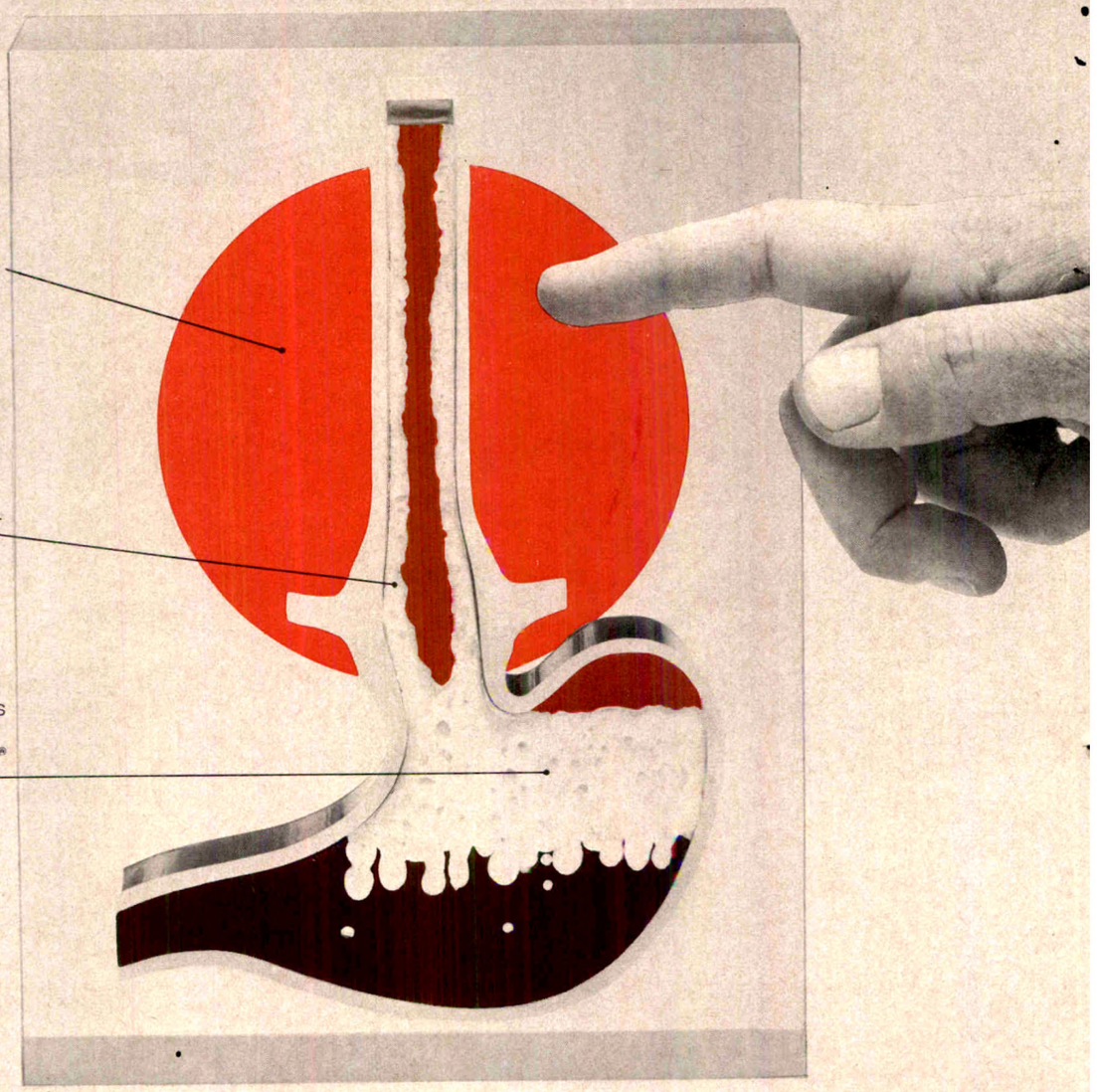
309462

"This is the real Heartburn Zone. This is where GAVISCON® works!"

The Real Heartburn Zone
When gastric juice refluxes into the esophagus, stomach contents irritate sensitive nerve endings in esophageal mucosa to produce the pain of heartburn.

Gaviscon Coats
The Gaviscon foam coating clings to esophageal mucosa for pinpoint neutralization of gastric contents which might reflux from the stomach.

Gaviscon Floats
In the cardia and fundus of the stomach, GAVISCON® FOAMTAB® tablets form a soft, viscous layer of floating antacid foam that precedes gastric contents refluxing into the esophagus.

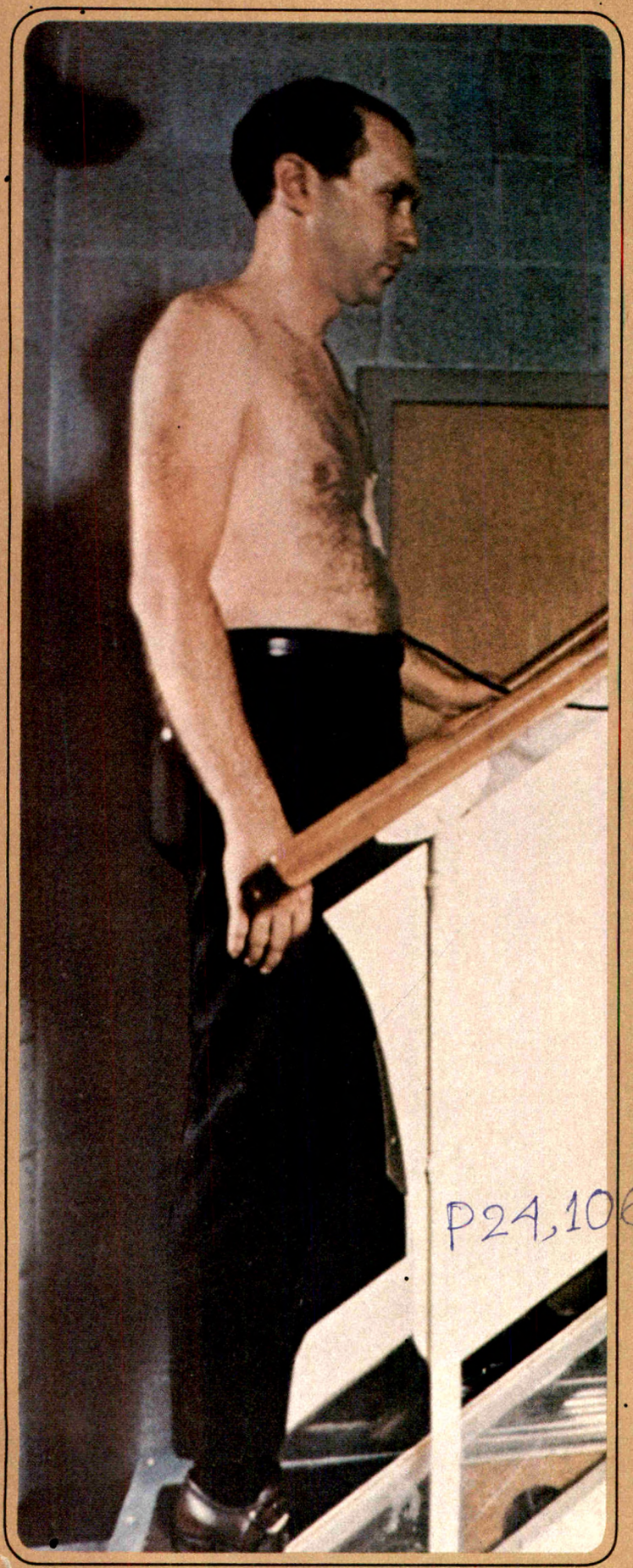


GAVISCON®

FOAMTAB®

(Alginic acid, 200 mg; aluminum hydroxide dried gel, 80 mg; magnesium trisilicate, 20 mg; sodium bicarbonate, 70 mg)
CHEWABLE ANTACID TABLETS for relief of heartburn accompanying hiatal hernia, gastroesophageal reflux, and esophagitis.

Another patient benefit product from MARION PHARMACEUTICAL DIVISION MARION LABORATORIES, INC. KANSAS CITY, MISSOURI 64137



tolerance to exercise improved for angina patients

INDICATIONS: For the prophylaxis and long-term management of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

PRECAUTIONS: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

SIDE EFFECTS: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound.

Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

SUPPLIED: 10 mg. chewable tablets. Bottles of 100. Also 5, 10 and 15 mg. scored tablets in bottles of 100. 10 mg. scored tablets also supplied in bottles of 1000.

Also available: Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital (Warning: may be habit-forming).

P24,106

Cardilate®
[erythrityl tetranitrate]

chewable tablets 10 mg.
t.i.d. or q.i.d. (p.r.n.)
an effect appears in approximately 5 minutes —total duration of effect up to 4 hours.

Complete literature available on request from Professional Services Dept. PML.

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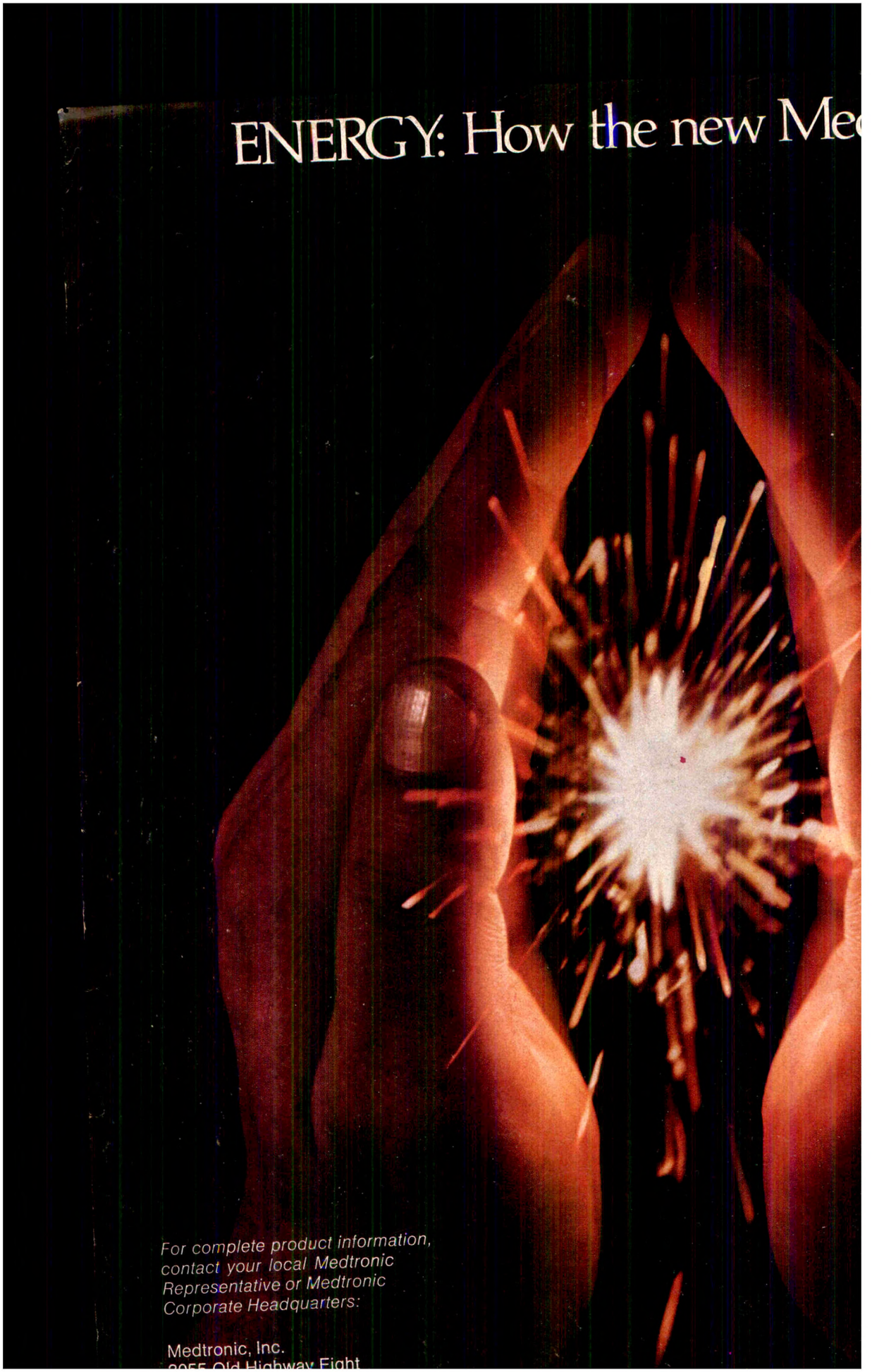
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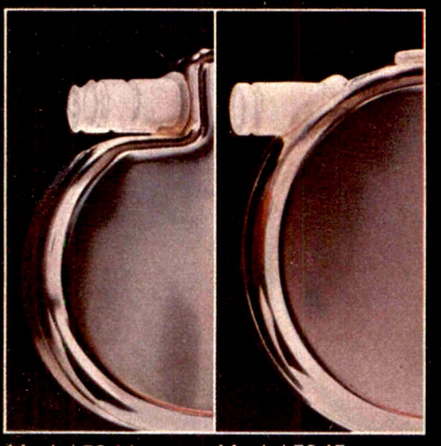
pacemakers conserve it.

The concept of Energy Conservation is based on one simple fact: lessen the drain on a power source and you extend its life.

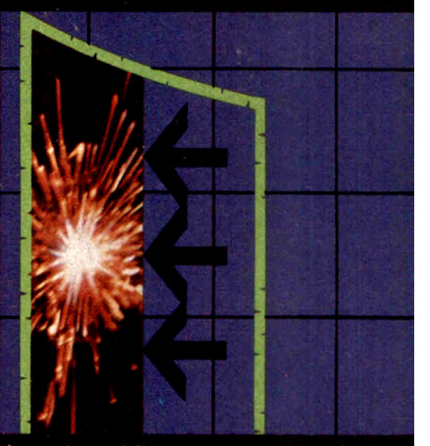
In the new Medtronic pacemakers, pulse width has been reduced to reduce the energy expenditure per pulse.

Less energy expended means longer projected life. It's that simple.



Model 5944— Bipolar Demand Pulse Generator

Model 5945— Unipolar Demand Pulse Generator



As pulse width narrows, projected life of the pulse generator is extended.

Another significant improvement combines the idea of energy compensation with a redundant cell depletion indicator. It works this way: when depletion of the first cell occurs the new Medtronic pulse generators show a decrease in rate similar to most other pulse generators. But, they also automatically increase pulse width when depletion occurs. This increase in pulse width compensates

The New Math of

It may increase diagnostic accuracy by an added 30%

If you're not testing for triglycerides, as well as for cholesterol, you may detect only 6 out of 10 patients with hyperlipidemia.[1]

If you're testing for <u>both</u> triglycerides and cholesterol, chances are you will detect more than 9 out of 10 patients (over 95%) with hyperlipidemia.[1]

The Proven Math

UP TO 35% REDUCTION OF ELEVATED CHOLESTEROL LEVELS

Cholesterol levels above 250 mg.% have decreased as much as 35%...and reductions up to 50% have been reported.[2-5]

UP TO 61% REDUCTION OF ELEVATED TRIGLYCERIDE LEVELS

Triglyceride levels above 150 mg.% have decreased as much as 61%...and reductions up to 90% have been reported.[2,5]

10 YEARS OF SUCCESSFUL OVERALL CLINICAL EXPERIENCE

Reliable cholesterol- and triglyceride-lowering effect persists as long as treatment is uninterrupted.[2,3] Xanthomata may regress or disappear completely.

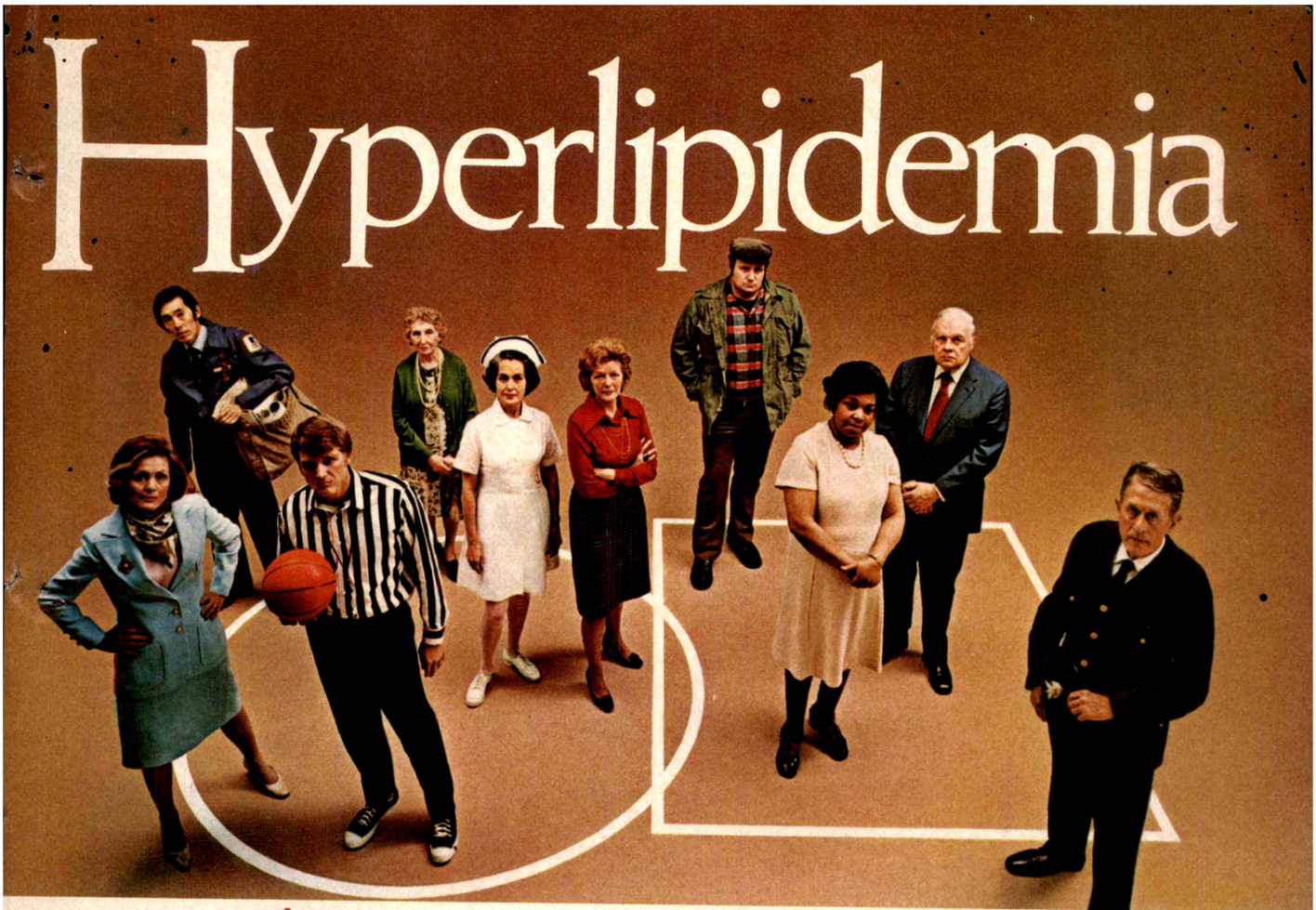
ONE ATROMID-S CAPSULE FOUR TIMES A DAY

A simple, well-accepted regimen that patients can stay with. Same dosage for *all* patients at *all* times.

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Hyperlipidemia



# of Atromid-S®

Brand of clofibrate

the most widely prescribed lipid-lowering agent–
significantly reduces
elevated levels of cholesterol and/or triglycerides,
not just cholesterol alone

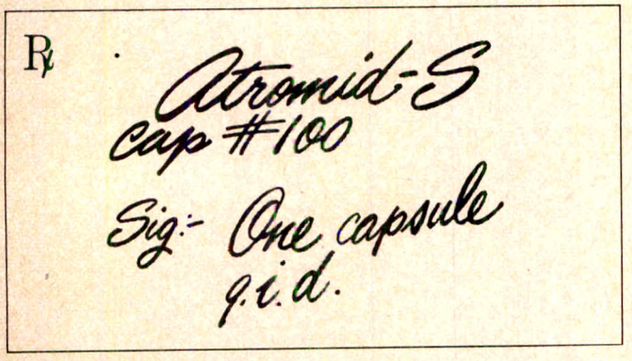
Hyperlipidemia/**Atromid-S®** (clofibrate) **Ayerst®**

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)

helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone



BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. Hepatic biopsies are usually within normal limits. These effects are usually reversible when the drug is discontinued. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

The physician should monitor the patient with complete blood counts since peripheral anemia and, more frequently, leukopenia have been reported in patients who have been taking clofibrate. Whether these are drug-related is unknown.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus. There have been occasional cases of dry, brittle hair and of alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: increased angina, peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision.

DOSAGE AND ADMINISTRATION: Adult Dose: The recommended dosage for adults is one capsule (500 mg.) four times daily.

In Children: Insufficient studies have been done in children to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. 2. Gelfand, M. L., and Garber, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. 3. Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. 4. Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. 5. Levy, R. I., and Fredrickson, D. S.: Amer. J. Cardiol. 22:576 (Oct.) 1968.

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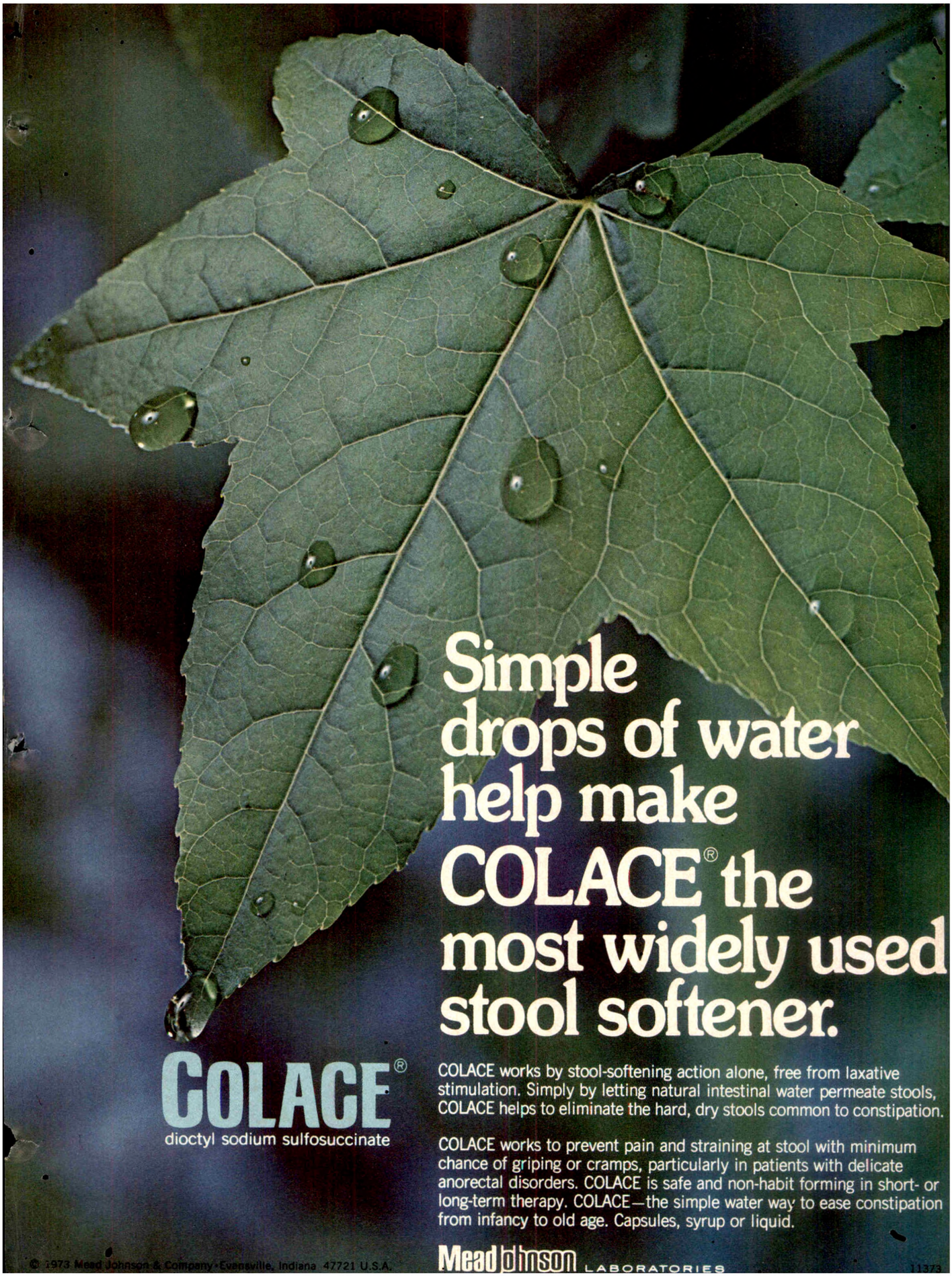
ATROMID-S® (clofibrate) is available in the United States by arrangement with Imperial Chemical Industries Ltd.



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COLACE works by stool-softening action alone, free from laxative stimulation. Simply by letting natural intestinal water permeate stools, COLACE helps to eliminate the hard, dry stools common to constipation.

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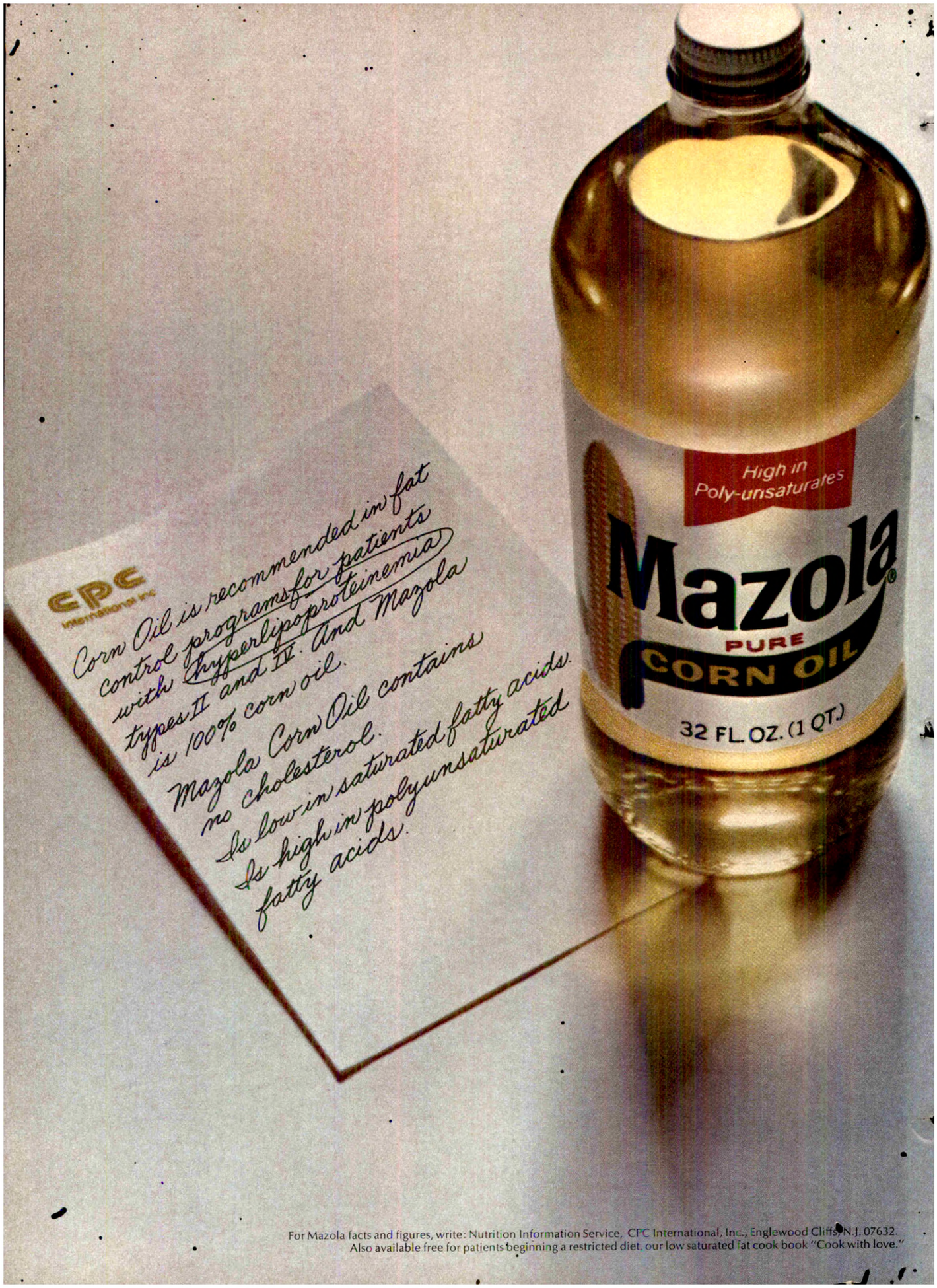

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Also available free for patients beginning a restricted diet, our low saturated fat cook book "Cook with love."

The Third Step in Angina.*

After the classic "2-Step" Test aids in a diagnosis of angina, sustained-release Nitro-Bid® (nitroglycerin) is a logical third step. Here's why.

In angina secondary to arteriosclerotic heart disease, sustained-release Nitro-Bid® (nitroglycerin) therapy assists in the "total management" of your patient.

Nitro-Bid capsules reduce sublingual nitroglycerin requirements as they reduce the number of angina attacks . . . increase exercise tolerance.

Sustained-release Nitro-Bid Plateau CAPS® provide a metered sequence of medication during the night to protect against nocturnal angina attack.

In titrating dosage, availability of different strengths "...is quite an asset..."[1]

Nitro-Bid 2.5 and Nitro-Bid 6.5 capsules afford two dosage strengths for convenience in increasing or decreasing dose to accommodate patient symptoms.

NITRO-BID® 2.5
(nitroglycerin 2.5 mg) Plateau CAPS®

NITRO-BID® 6.5
(nitroglycerin 6.5 mg) Plateau CAPS®

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

*"Possibly" effective:
For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.

Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.

Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.

Dosage: One capsule two or three times daily at 8 to 12 hour intervals.

Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY MISSOURI 64137

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The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

Persantine — over a decade of use

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Persantine — give enough — long enough

The recommended dosage: 50 mg. t.i.d. at least one hour before meals. *Give enough, long enough* — several weeks or longer of continuous therapy may be needed to see response.

Persantine® Tablets of 25 mg.
dipyridamole

the non-nitrate
coronary vasodilator

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

Taoist Eye-Heart Pathway
Representation of inner man as conceived by Taoism. Note the connecting line running from the eye to the heart. The eye-heart pathway may well allude to the Taoist principles of the right path delineated by Confucian philosophy—the path of virtuous conduct.

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4 reasons why you should continue to recommend Fleischmann's Margarine as part of a low saturated fat diet.

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Each pound contains almost one cup liquid corn oil.

Clinical studies show corn oil is unsurpassed among vegetable oils in lowering serum cholesterol.

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For years you've known about the excellent P/S ratio of Fleischmann's® Margarine; it's high in polyunsaturates, low in saturated fat. Fleischmann's is made from 100% corn oil; almost one cup is important liquid corn oil. And clinical tests have shown corn oil is unsurpassed among vegetable oils for lowering serum cholesterol.[1-9] And because Fleischmann's is made from 100% corn oil, it tastes delicious.

It is reported that the natural plant sterols of corn oil, in addition to its excellent P/S ratio, may play an important role in corn oil's hypocholesteremic effect. Studies indicate that natural plant sterols exert an independent suppressant effect on serum cholesterol.[6,7,10] Corn oil has a higher content of these sterols than other commonly used vegetable oils. This unique combination of factors, P/S ratio and plant sterols, is believed responsible for corn oil being unsurpassed in lowering serum cholesterol.[4,5]

Fleischmann's Margarine can be recommended with confidence for low cholesterol/low saturated fat diets because it is made from 100% corn oil. Fleischmann's makes sensible eating delicious.

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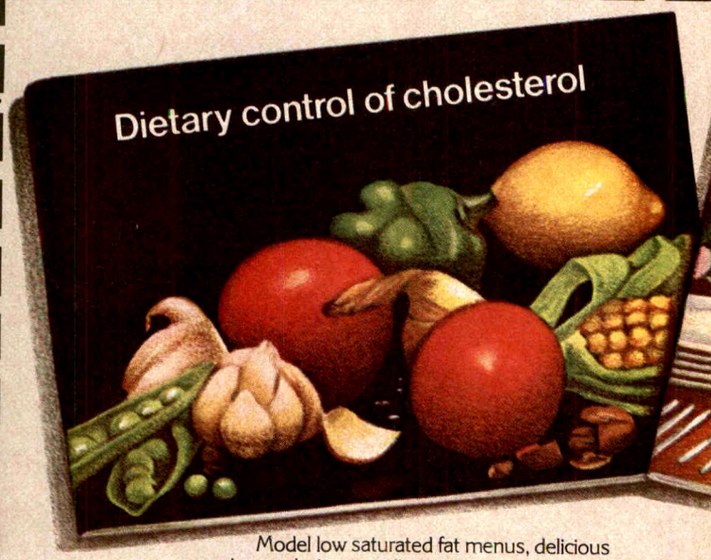

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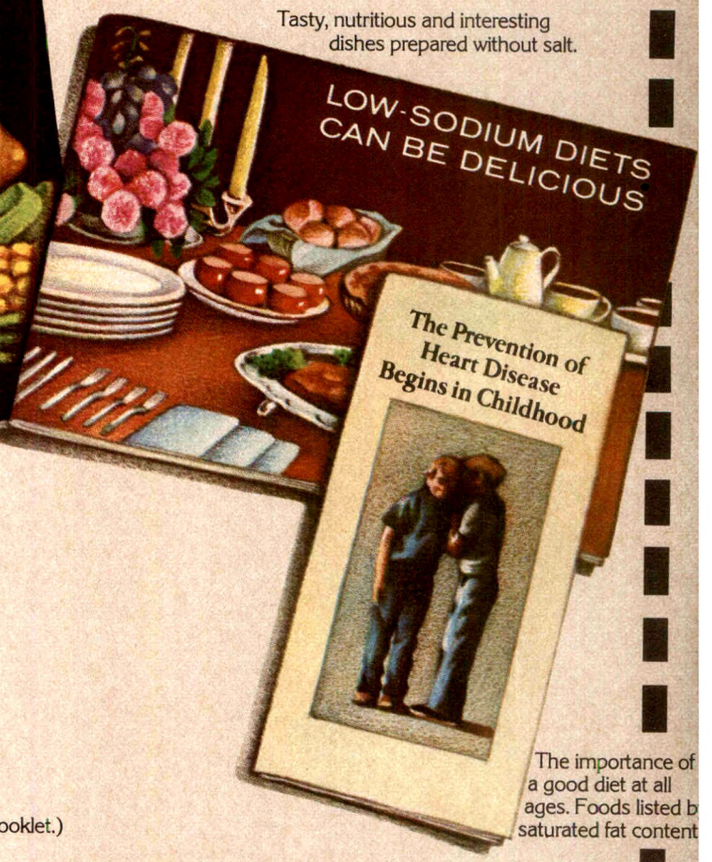

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1. Hegsted, D.M., et al: *Amer. J. Clin. Nutr.* 17:281, Nov. 1965. **2.** Perkins, R., et al: *JAMA* 169:1731, Apr. 11, 1959. **3.** Jolliffe, N.: *Metabolism* 10:497, July 1961. **4.** Grande, F., et al: *Proc. Soc. Exp. Biol. Med.* 98:436, June 1958. **5.** Armstrong, W.D., et al: *Proc. Soc. Exp. Biol. Med.* 96:302, Nov. 1957. **6.** Farquhar, J.W., and Sokolow, M.: *Circulation* 17:890, May 1958. **7.** Beveridge, J.M.R., et al: *J. Nutr.* 83:119, June 1964. **8.** Brown, H.B., et al: *JAMA* 196:205, Apr. 18, 1966. **9.** Stare, F.J.: *J. Amer. Diet. A.* 48-88, Feb. 1966. **10.** Krantz, J.C., Jr. and Carr, C.J.: *Pharmacologic Principles of Medical Practice,* 5th ed., Williams & Wilkins, Baltimore 1961, p. 1457.

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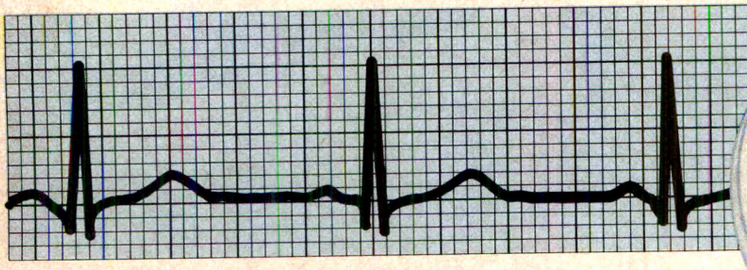

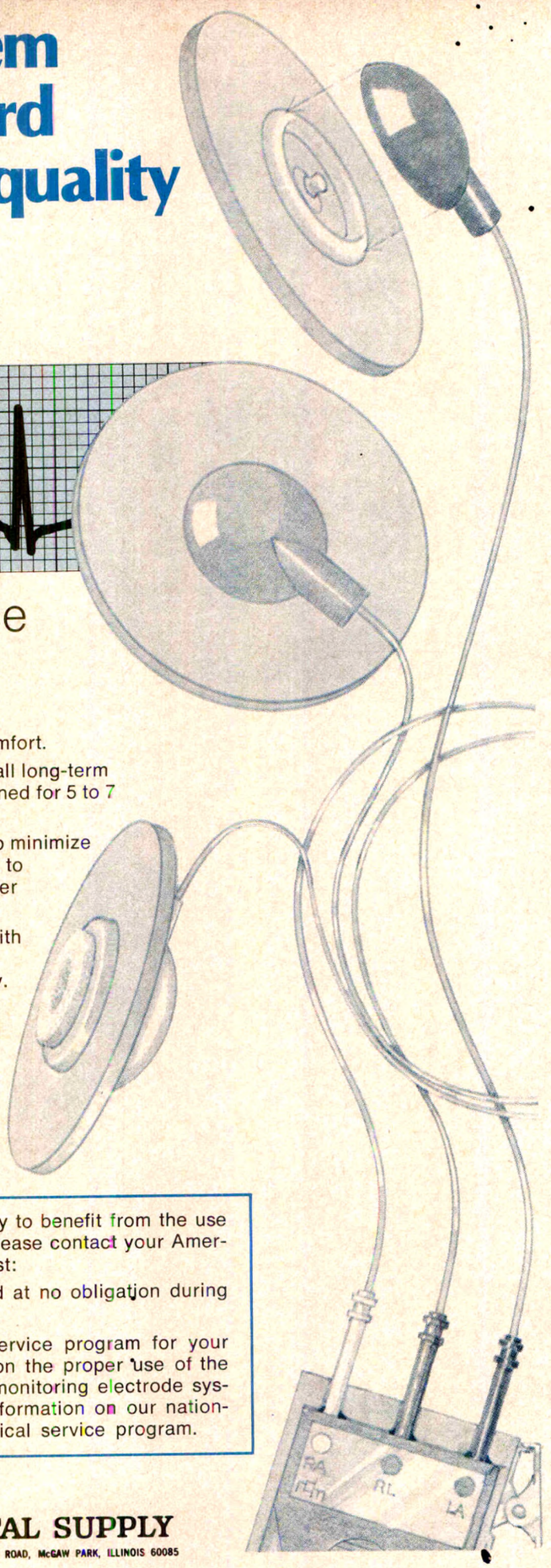

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Transient Ischemic Attacks (TIA's) are another signal of impending stroke that is particularly ominous. In fact, 33% of patients with TIA's will develop a severe neurological deficit within 5 years.*

For such patients, PAVABID® (papaverine HCl) vasodilatation helps to preserve cerebral circulation. By reducing arterial tone, Pavabid therapy helps block vasospasm that can result in neurological damage.

*Meyer, J. S., and Gilroy, J.: *Medical Neurology*, ed 1, The Macmillan Co., 1969, p 495.

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(papaverine HCl, 150 mg.) Plateau CAPS®

Pavabid® Plateau CAPS® (Papaverine HCl, 150 mg.)—Each capsule contains papaverine hydrochloride, 150 mg. in a special base for prolonged therapeutic effect. *Indications:* For the relief of cerebral and peripheral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias. *Dosage:* One capsule every 12 hours. In difficult cases, administration may be increased to one capsule every 8 hours, or two capsules every 12 hours. *Precaution:* Use with caution in patients with glaucoma. Hepatic hypersensitivity has been reported with gastrointestinal symptoms, jaundice, eosinophilia and altered liver function tests. Discontinue medication if these occur. *Side effects:* Infrequently reported side effects of papaverine include nausea, abdominal distress, anorexia, constipation, malaise, drowsiness, vertigo, sweating and headache, diarrhea and skin rash.

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PUBLISHED TO CORRECT A PREVIOUS ADVERTISEMENT WHICH THE FOOD AND DRUG ADMINISTRATION CONSIDERED MISLEADING

QUESTRAN®
(CHOLESTYRAMINE)

EACH DOSE CONTAINS 4G. OF CHOLESTYRAMINE RESIN IN 9G. OF QUESTRAN.

THE FOOD AND DRUG ADMINISTRATION CONSIDERS MISLEADING OUR ADVERTISING FOR QUESTRAN (CHOLESTYRAMINE RESIN) THAT APPEARED IN THIS JOURNAL.

THE FDA STATES THAT THE AD:

- FAILED TO ADEQUATELY EMPHASIZE THE DRUG'S LIMITATIONS THAT QUESTRAN IS INDICATED AS *ADJUNCTIVE* THERAPY TO *DIET* IN LOWERING ELEVATED CHOLESTEROL LEVELS DUE *ONLY* TO PRIMARY TYPE II HYPERLIPOPROTEINEMIA AND MAY *INCREASE* CHOLESTEROL AND TRIGLYCERIDE LEVELS IN PATIENTS WITH TYPES I, III, IV AND V.

- IMPLIED THAT QUESTRAN IS *BOTH* SAFER AND MORE EFFECTIVE THAN ANY OTHER AVAILABLE ANTILIPEMIC THERAPY FOR ITS INDICATED USE WHEN THE FACT IS THAT THIS HAS NOT BEEN ESTABLISHED BY COMPARATIVE STUDIES WITH ALL OTHER EFFECTIVE DRUGS IN TYPE II HYPERLIPOPROTEINEMIA.

- FAILED TO ADEQUATELY EMPHASIZE THAT IT HAS NOT BEEN ESTABLISHED WHETHER DRUG-INDUCED LOWERING OF SERUM CHOLESTEROL OR OTHER LIPID LEVELS HAS A DETRIMENTAL, A BENEFICIAL OR NO EFFECT ON THE MORBIDITY OR MORTALITY DUE TO ATHEROSCLEROSIS OR CORONARY HEART DISEASE.

THE ADVERTISEMENT HAS BEEN DISCONTINUED BY DIRECTION OF THE FOOD AND DRUG ADMINISTRATION.

SAFETY CONSIDERATIONS:

QUESTRAN®
(CHOLESTYRAMINE)

IMPORTANT NOTE: **IT HAS NOT BEEN ESTABLISHED WHETHER DRUG-INDUCED LOWERING OF SERUM CHOLESTEROL OR OTHER LIPID LEVELS HAS A DETRIMENTAL, A BENEFICIAL, OR NO EFFECT ON THE MORBIDITY OR MORTALITY DUE TO ATHEROSCLEROSIS OR CORONARY HEART DISEASE.**

CONTRAINDICATIONS

INDIVIDUALS HYPERSENSITIVE TO ANY OF ITS COMPONENTS AND PATIENTS WITH COMPLETE BILIARY OBSTRUCTION.

WARNINGS

DO NOT TAKE IN DRY FORM. MIX WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

USE IN PREGNANCY

SAFE USE BY PREGNANT AND LACTATING WOMEN AND FETUS HAS NOT BEEN ESTABLISHED. WEIGH HAZARDS AGAINST POTENTIAL BENEFITS OF DRUG THERAPY.

USE IN CHILDREN

PRACTICAL DOSAGE SCHEDULE HAS NOT BEEN ESTABLISHED FOR INFANTS AND CHILDREN. LONG TERM DRUG ADMINISTRATION AND EFFECT IN MAINTAINING LOWERED CHOLESTEROL LEVELS UNKNOWN IN PEDIATRIC PATIENTS.

PRECAUTIONS

SINCE CHOLESTYRAMINE RESIN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR FOUR TO SIX HOURS AFTER TO AVOID IMPEDING THEIR ABSORPTION.

QUESTRAN SEQUESTERS BILE ACIDS, THEREFORE IT MAY INTERFERE WITH NORMAL FAT ABSORPTION AND THUS PREVENT ABSORPTION OF FAT SOLUBLE VITAMINS SUCH AS A, D AND K, AND AS AN ANION EXCHANGE RESIN, IT HAS A STRONG AFFINITY FOR ACIDIC MATERIALS AND MAY ALSO ABSORB NEUTRAL OR BASIC MATERIALS. CHOLESTYRAMINE RESIN MAY DELAY OR REDUCE ABSORPTION OF CONCOMITANT ORAL MEDICATION SUCH AS PHENYLBUTAZONE, WARFARIN, CHLOROTHIAZIDE (ACIDIC), TETRACYCLINE, PHENOBARBITAL, THYROID, THYROXINE PREPARATIONS, AND DIGITALIS. DISCONTINUANCE OF QUESTRAN COULD POSE A HAZARD TO HEALTH IF A POTENTIALLY TOXIC DRUG SUCH AS DIGITALIS HAS BEEN TITRATED TO A MAINTENANCE LEVEL WHILE THE PATIENT WAS TAKING QUESTRAN.

CHECK SERUM TRIGLYCERIDE LEVELS PERIODICALLY TO ENSURE THAT SIGNIFICANT CHANGES HAVE NOT OCCURRED, IN NORMAL FAT DIGESTION.

PROLONGED USE MAY PRODUCE HYPERCHLOREMIC ACIDOSIS, ESPECIALLY IN YOUNGER AND SMALLER PATIENTS WHERE THE RELATIVE DOSAGE MAY BE HIGHER.

WHEN USED AS A CHOLESTEROL LOWERING AGENT, GASTROINTESTINAL DYSFUNCTION SHOULD BE EVALUATED PRIOR TO USE.

ADVERSE REACTIONS

CONSTIPATION, IMPACTION, HEMORRHOIDS, ABDOMINAL DISCOMFORT, FLATULENCE, NAUSEA, VOMITING, DIARRHEA, HEART BURN, ANOREXIA, INDIGESTIVE FEELING, STEATORRHEA, BLEEDING TENDENCIES (HYPOPROTHROMBINEMIA—VITAMIN K DEFICIENCY), VITAMIN A AND D DEFICIENCIES, RASH, HYPERCHLOREMIC ACIDOSIS, OSTEOPOROSIS, CALCIFICATION, INCLUDING BILIARY COLIC.

HEMATOLOGIC—DECREASED PROTHROMBIN TIME, ECCHYMOSIS, ANEMIA.

CARDIOVASCULAR—CLAUDICATION, XANTHOMAS OF HANDS AND FINGERS, ANGINA, ARTERITIS, THROMBOPHLEBITIS, MYOCARDIAL INFARCTION, MYOCARDIAL ISCHEMIA, INCREASED POSTPRANDIAL ANGINA, CHEST PAINS.

HYPERSENSITIVITY—URTICARIA, ASTHMA, WHEEZING, SHORTNESS OF BREATH.

MUSCULOSKELETAL—BACKACHE, MUSCLE AND JOINT PAINS, ARTHRITIS.

NEUROLOGIC—HEADACHE, ANXIETY, VERTIGO, DIZZINESS, FATIGUE, TINNITUS, SYNCOPE, DROWSINESS, FEMORAL NERVE PAIN, PARESTHESIA.

EYE—ARCUS JUVENILIS, UVEITIS.

RENAL—HEMATURIA, DYSURIA, BURNT ODOR TO URINE, DIURESIS.

MISCELLANEOUS—WEIGHT LOSS, WEIGHT GAIN, INCREASED LIBIDO, SWOLLEN GLANDS, EDEMA, DENTAL BLEEDING.

OTHER EVENTS REPORTED IN PATIENTS TAKING QUESTRAN INCLUDE: GI-RECTAL BLEEDING, BLACK STOOLS, HEMORRHOIDAL BLEEDING, BLEEDING FROM KNOWN DUODENAL ULCER, DYSPHAGIA, HICCUPS, ULCER ATTACK, SOUR TASTE, PANCREATITIS, RECTAL PAIN, DIVERTICULITIS.

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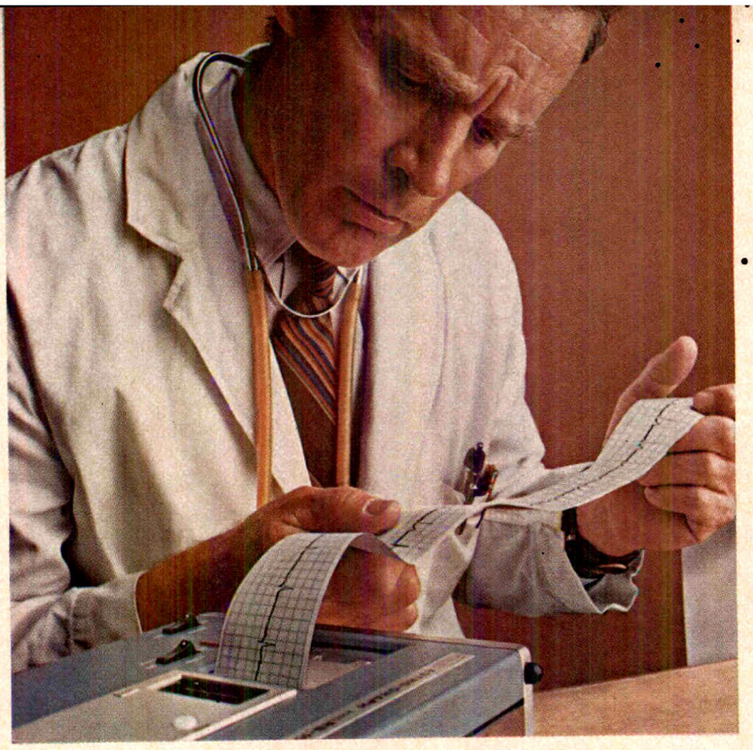
When cardiac complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on heart function

Excessive anxiety is one of a combination of factors that may trigger a series of maladaptive functional reactions which can generate further anxiety. Often involved in this vicious circle are some cardiac arrhythmias, paroxysmal supraventricular tachycardia and premature systoles. When these symptoms resemble those associated with actual organic disease, the overanxious patient needs reassurance that they have no

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

organic basis and that reduction of excessive anxiety and emotional overreaction would be medically beneficial.

The benefits of antianxiety therapy

Antianxiety medication, when used to complement counseling and reassurance, should be both effective and comparatively free from undesirable side effects. More than 13 years of extensive clinical experience has demonstrated that Librium (chlordiazepoxide HCl) fulfills these requirements with a high degree of consistency. Because of its wide margin of safety, Librium may generally be administered for extended periods, at the physician's discretion, without diminution of effect or need for increase in dosage. (See summary of prescribing information.) If cardiovascular drugs are necessary, Librium is used concomitantly whenever anxiety is a clinically significant factor. (See Precautions.) Librium should be discontinued when anxiety has been reduced to appropriate levels.

For relief of excessive anxiety adjunctive

Librium® 10 mg
(chlordiazepoxide HCl)
1 or 2 capsules t.i.d./q.i.d.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

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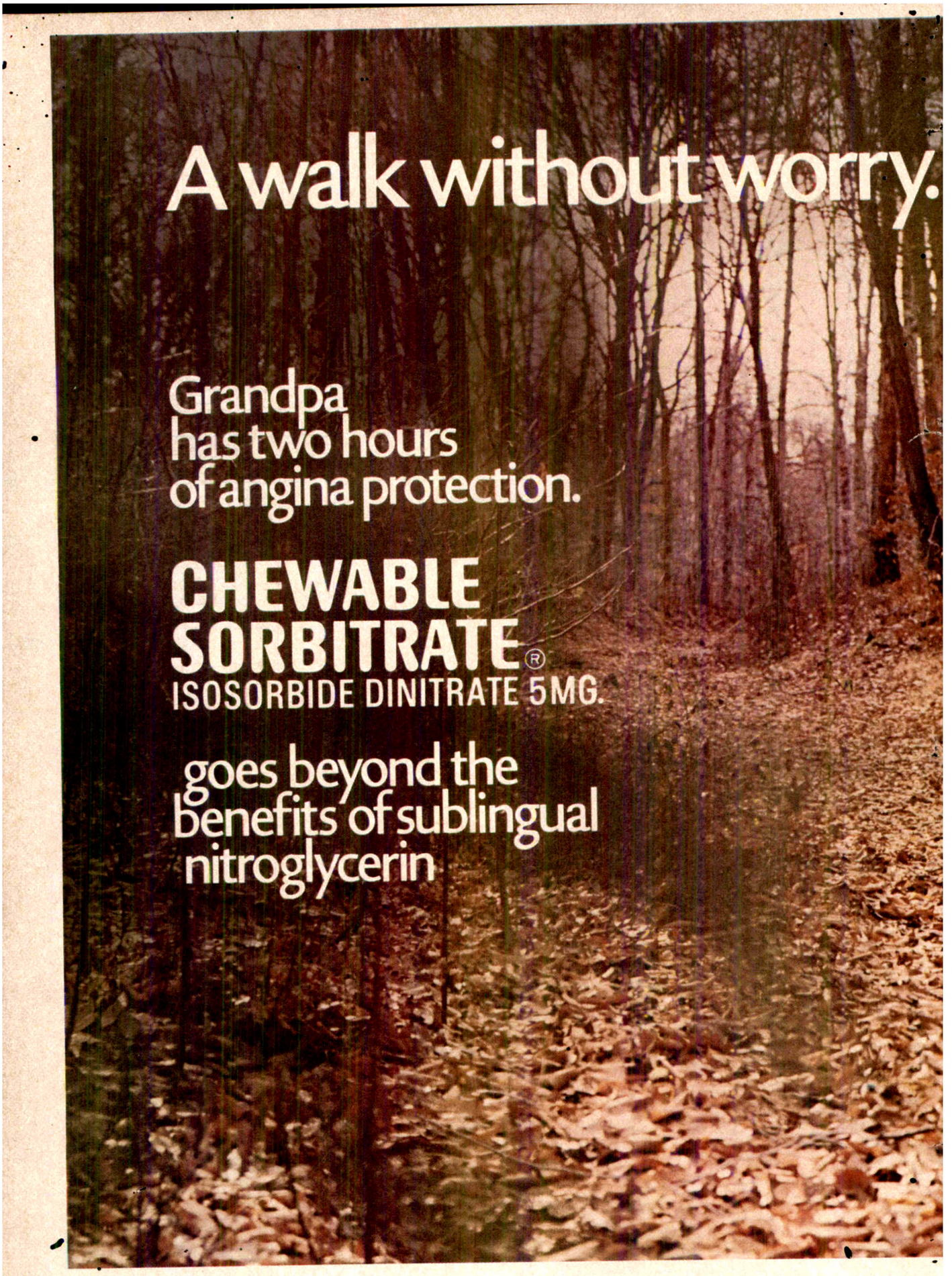
in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.


A walk without worry.
Grandpa
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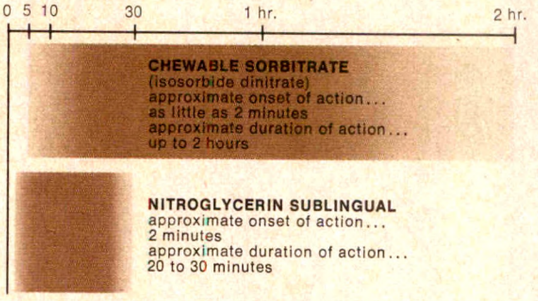
nitroglycerin

For up to two hours of protection, your angina patient needs *more* than sublingual nitroglycerin. And Chewable Sorbitrate provides more.

☐ Acts almost as fast as nitroglycerin... lasts about 4 times as long.



☐ More stable in air than sublingual nitroglycerin: it can be stored or carried with no significant loss of potency.

☐ And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Scheaule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS | Div. of ICI America Inc.
WILMINGTON, DEL. 19899

The unique

Kato® Powder

potassium chloride supplement with the natural tomato juice flavor

Description: Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 Gm KCl) per measured dose with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink.

Indications: The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

Contraindications: Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, hyperkalemia from any cause.

Precautions: Kato Powder is a concentrate and should be taken only after reconstituting with water as directed. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible accurately to assess the extent of potassium depletion, or the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

Adverse Reactions: Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Toxicity: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 Gm dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

Administration and Dosage: Mix with water to make a pleasant tomato juice drink. The unit dose packet and the dose-measure supplied in the can each provide 20 mEq of potassium. Usual adult dose—1 packet or 1 measure of Kato Powder mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

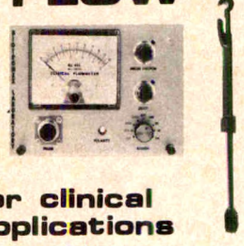
How Supplied:

Carton of 30 unit dose packets, 20 mEq each.

8 oz can (40 doses) with 20 mEq dose-measure.

Ingram Pharmaceutical Company / San Francisco, Ca 94111

BLOOD FLOW



for clinical applications

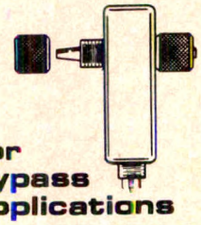
- Designed for clinical O.R. or cath lab use
- Easily applied handle-type probe
- Patient safety assured through isolation circuitry
- Simple to operate - minimum controls - direct meter readout in milliliters per minute

FLOW PROBES

for clinical applications

- Convenient, handle-type probe with positive capture slide
- Designed for O.R. and cath lab use
- For rapid analysis of flow through exposed blood vessels
- Use with Biotronex clinical blood flowmeter

FLOW PROBES



for bypass applications

- Use with heart-lung machine, artificial kidney or similar systems
- Iron core construction provides high sensitivity and accuracy
- Operates with BLI research and clinical blood flowmeters
- Available in sizes to fit most tubing

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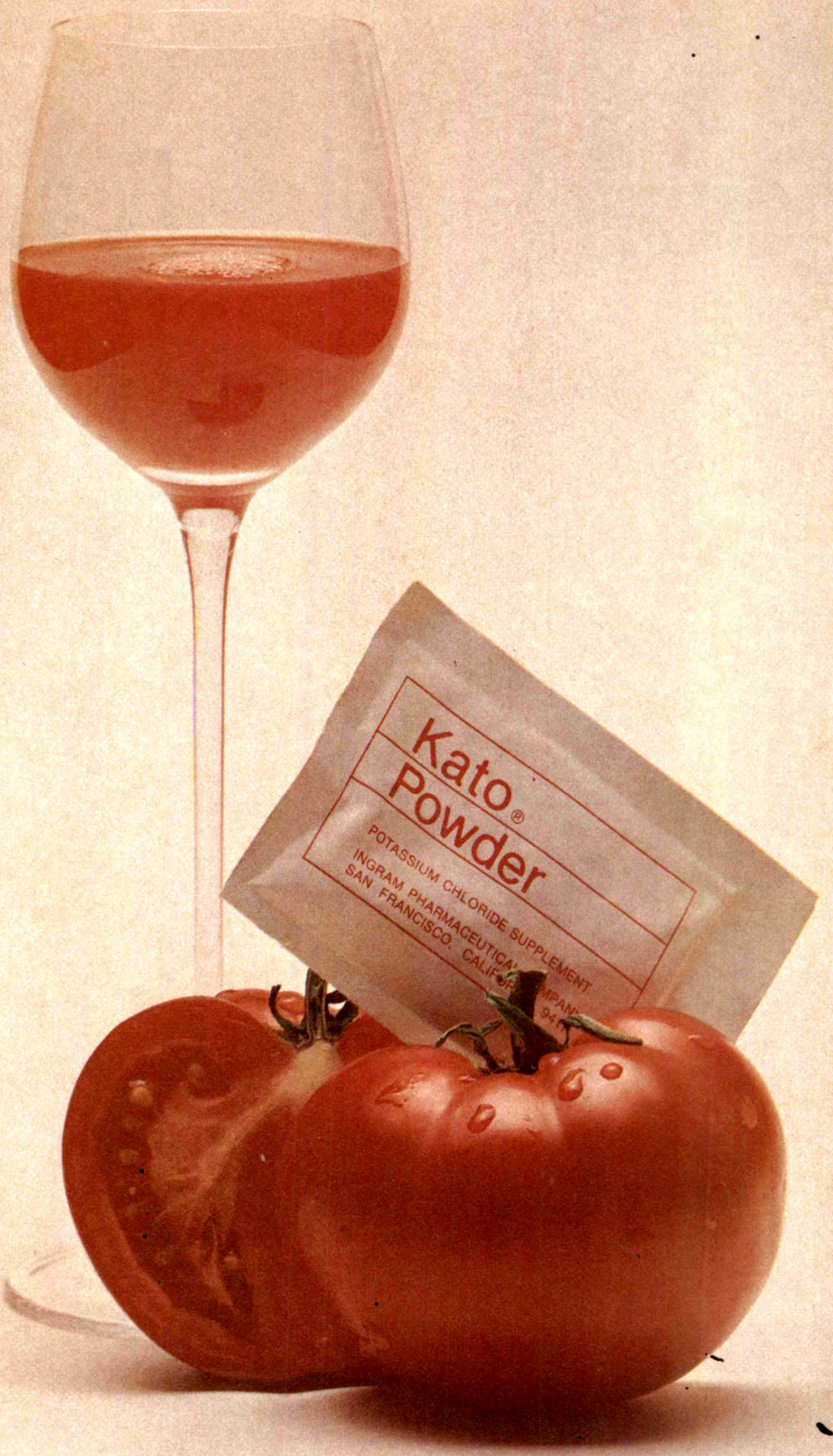
in potassium therapy

Kato is a Natural

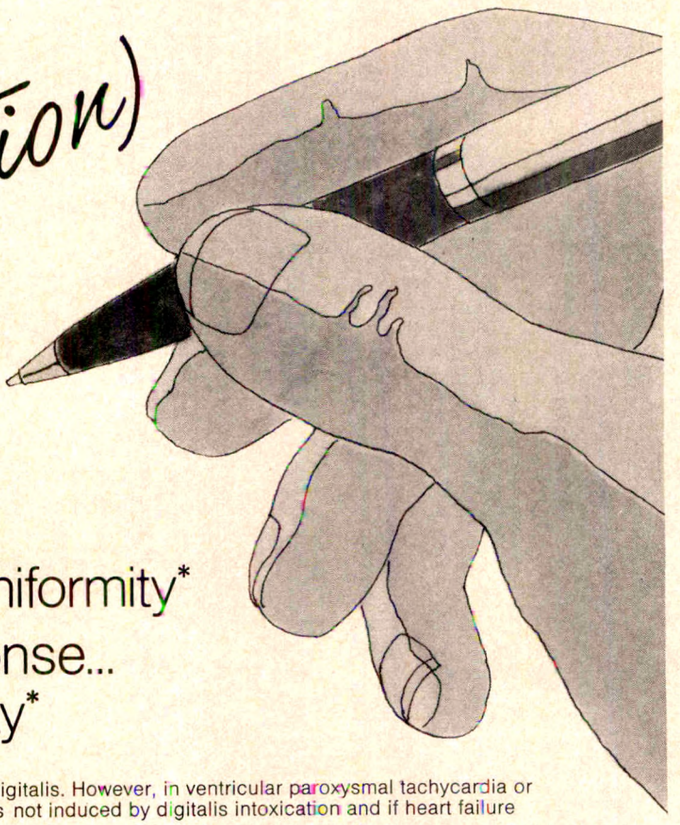


Kato Powder is KCl blended with natural tomato powder and subtle spices. Mixed with a mere 2 ounces of cold water, it provides a dose of potassium chloride in a good tasting low sodium tomato juice drink. Refreshingly different. Patients take it and like it!

Lanoxin

[digoxin]

(no substitution)



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precision quality control...

- assured tablet content uniformity*

predictable patient response...

- proven biologic availability*

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

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JANUARY 1974

The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 1

CLINICAL STUDIES

Comparison of Biplane and Single Plane Left Ventriculograms in Patients with Coronary Artery Disease

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Fifty patients with coronary artery disease were studied with biplane left cineventriculography (right and left anterior oblique views). Volumetric analyses were compared with those of 10 normal patients also studied with simultaneous biplane ventriculography. In normal subjects there was good agreement between minor diameters in the right and left anterior oblique views, and between ventricular volumes and ejection fractions determined by single plane and biplane techniques. In patients with coronary artery disease there was more scatter in these values, especially when asynergy was present. Loss of ventricular symmetry probably explains this disparity. By providing visualization of all five zones of the left ventricular wall, the biplane technique allowed a comprehensive evaluation of ventricular asynergy and overall function.

The clinical profile of the 50 patients with coronary artery disease demonstrated that optimal candidates for biplane ventriculography are patients with prior myocardial infarction, left ventricular enlargement and clinical evidence of abnormal hemodynamic status.

The animal experiments of Tennant and Wiggers[1] and the subsequent clinical observations of Harrison[2] have stimulated interest in abnormal ventricular wall motion in coronary artery disease. Investigations using noninvasive techniques have included analysis of precordial pulsations and heart sounds[3-5] as well as more sophisticated measures such as echocardiography,[6] scintiphotography[7] and radarkymography.[8] The most recent standard of reference has been the study of left ventricular wall motion by left cineventriculography.[9-12] Single plane projections have been used in most reported studies. This communication assesses the comparative value of single and biplane ventriculography in detecting abnormal wall motion and determining ventricular volumes and ejection fractions in patients with coronary artery disease.

From the Cardiovascular Division, Department of Medicine and the Department of Radiology, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass. This study was supported in part by U. S. Public Health Service Grants PO-1 HE-11306, IT-1 HE-5679, HE-11668, HE-05832 and GM-18674. Manuscript accepted June 27, 1973.

Address for reprints: Peter F. Cohn, MD, Cardiovascular Division, Department of Medicine, Peter Bent Brigham Hospital, 721 Huntington Ave., Boston, Mass. 02115.

Methods

Patient selection: Sixty patients with a syndrome of chest pain were classified in two groups. Group 1 consisted of 10 consecutive patients with

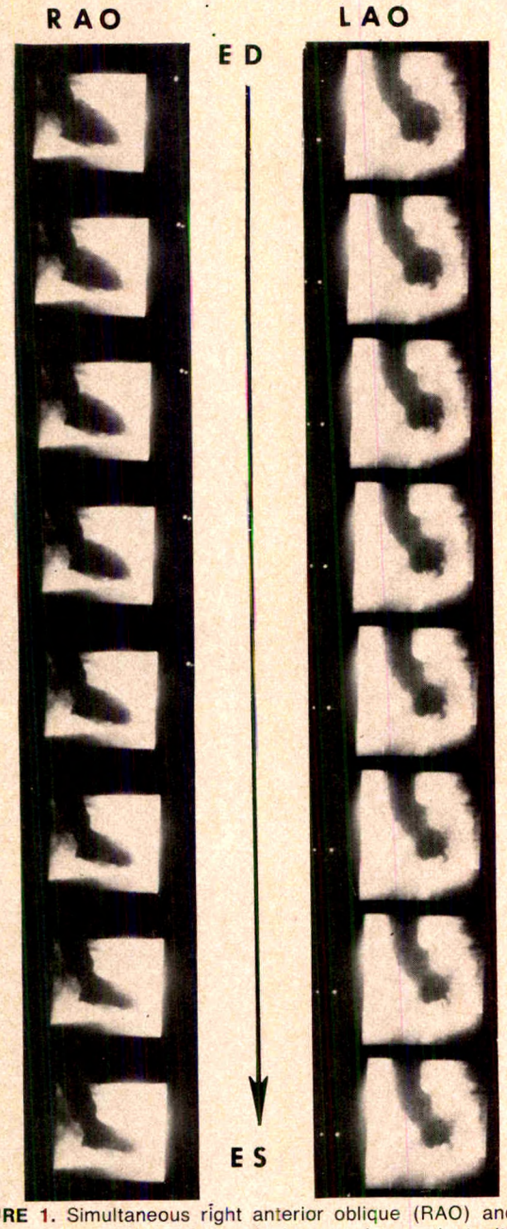

FIGURE 1. Simultaneous right anterior oblique (RAO) and left anterior oblique (LAO) left ventriculograms in a patient with obstructive disease of the right coronary and left anterior descending arteries. The sequence is from end-diastole (ED) to end-systole (ES). Asynergy is most marked in the right anterior oblique view and mainly involves the apical and anterior segments. The left anterior oblique view demonstrates good wall motion, especially in the posterolateral segment. The ejection fraction calculated from volumes determined in the biplane projection was 51 percent, compared to 39 percent when calculated from volumes determined in the right anterior oblique projection.

normal coronary arteriograms, normal hemodynamic status and normal biplane left ventriculograms. They served as control subjects for evaluating left ventricular volumes, ejection fractions and wall motion. Group 2 comprised 50 consecutive patients with demonstrated coronary artery disease. None of these 50 patients had concomitant rheumatic, pericardial or congenital heart disease.

Evidence of prior transmural infarction was determined by standard enzymatic and electrocardiographic criteria.[13] Evidence of left ventricular enlargement was determined from the posteroanterior, lateral and left anterior oblique views of a four position cardiac series, using standard radiologic criteria.[13]

Catheterization and angiographic procedures: Catheterization procedures were similar to those previously reported from our laboratory.[9,10] Left ventricular end-diastolic pressure was measured at high gain (normal value ≤12 mm Hg). Cardiac output was determined by the indocyanine green dye technique (normal value ≥2.5 liters/min per m^2). Selective coronary cineangiograms were obtained by either the Sones or Judkins technique on 16 mm Ilford Pan F or Kodak Plus-X film with General Electric or Siemens 6 to 9 inch dual field, image-intensifier X-ray systems.

Simultaneous left ventricular cineangiograms (at 100 to 200 frames/sec) were obtained with multiple-hole catheters using power injections and 40 to 50 ml of 76 percent meglumine sodium diatrizoate. The biplane projections were 30° in the right and 60° in the left anterior oblique (RAO, LAO) views when the 9 inch mode was used (Fig. 1). All ventriculograms were interpreted by the same two investigators who reached a consensus without knowledge of the patients' coronary anatomic data. The term *asynergy* refers to all localized abnormalities of systolic wall motion (with septal asynergy referring to asynergy of both the anterior and posterior septum), and the method of interpreting these various patterns is that of Herman et al.[10] Ventricular volumes and ejection fractions were calculated from sequential end-diastolic and end-systolic silhouettes (Fig. 2), using a grid calibration technique and single plane (right anterior oblique) and biplane volumetric formulas adapted from those of Dodge et al.[14]: single plane volume = $\pi/6\,DRAO^2 \times LRAO$ with D the calculated minor diameter and L the measured length to base diameter; bi-

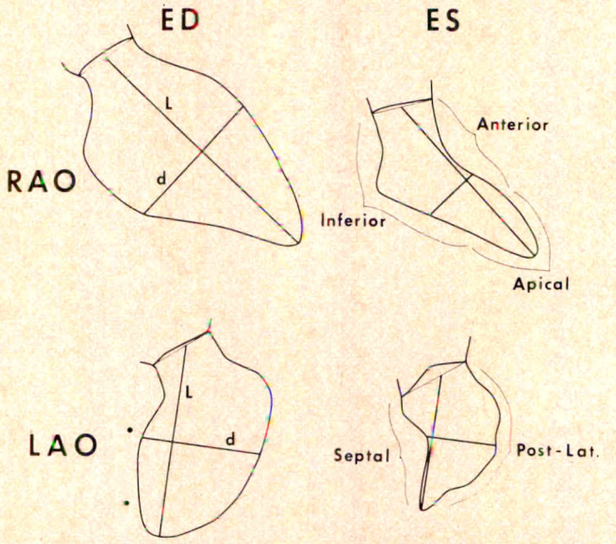

FIGURE 2. End-diastolic (ED) and end-systolic (ES) silhouettes drawn from simultaneous right anterior oblique (RAO) and left anterior oblique (LAO) left ventriculograms. The five segments of left ventricular wall are depicted as well as the method for measuring major (L) and minor (d) ellipsoid diameters. When the minor diameter is calculated, the formula used is D = 4 Area/πL (see text). Post-Lat. = posterolateral.

plane volume = $\pi/6$ DRAO × DLAO × LRAO (unless LLAO longer). In the present study D was calculated from the formula D = 4 Area/πL . L was always measured from the middle of the aortic valve to the apex in both projections and in nearly all cases was the longest major diameter. This technique allowed measurement of a three-dimensional figure in which the minor diameters are perpendicular to each other in the same plane. Analysis was limited to regularly conducted beats occurring no later than four cycles after complete opacification. Because of the frequency of wall motion abnormalities in this study, no attempt was made to correct angiographic volume to true volume by use of barium-filled ventricular casts.

Results

Clinical, hemodynamic and arteriographic variables associated with asynergy: The frequency of asynergy in the patients with coronary artery disease is shown in Table I. Certain variables were more often associated with asynergy than were others: Asynergy was present in 4 of 4 patients (100 percent) with chronic R–ST segment elevation on the electrocardiogram, 22 of 23 (96 percent) with increased left ventricular end-diastolic pressure, 22 of 25 (88 percent) with left ventricular enlargement, 32 of 40 (80 percent) with a prior myocardial infarction and 24 of 32 (75 percent) with multivessel coronary artery disease. Approximately 50 percent of the patients with normal ventricular size, normal left ventricular hemodynamics and single-vessel disease also exhibited asynergy, and asynergy was present in 2 of 10 patients with a completely normal resting electrocardiogram and no history of infarction.

Value of left anterior oblique view in assessing asynergy: Posterolateral wall motion can readily be assessed in the left anterior oblique view, but septal motion is sometimes obscured by overlying apical segments of the left ventricle. This is especially true when angiographic contrast medium is concentrated in an akinetic apex and prevents visualization of the posterior septum. With this reservation, the following observations were made in patients with coronary artery disease (Table II): (1) Fifteen patients (30 percent) had normal wall motion in both views; (2) 35 patients (70 percent) had abnormal motion in the right anterior oblique view, but 10 of these had normal motion in the left anterior oblique view; (3) 10 patients (20 percent) had isolated asynergy in a single zone of the right anterior oblique projection; no patient had isolated asynergy in the left anterior oblique view.

These findings indicate that wall motion in the left anterior oblique view more often appeared to be normal than motion in the corresponding right anterior oblique view. Furthermore, certain patterns of asynergy emerged. Some degree of septal asynergy was present in 25 patients. All of these patients had anterior or apical zone asynergy; similarly, all six patients with posterolateral asynergy had inferior asynergy combined with anteroapical disease (global asynergy). The converse was not true, however. As noted, many patients with anteroapical or inferior asynergy had normal posterolateral motion. Five of six patients (83 percent) with posterolateral asynergy had significant disease of the left circumflex artery. But obstructive disease was generally much less common in the circumflex system than in either the left anterior descending or right coronary arteries.

TABLE I

Clinical, Hemodynamic and Arteriographic Correlations in 50 Patients with Coronary Artery Disease

	Total	Normal Wall Motion	Asynergy
Clinical:	50	15	35
Normal electrocardiogram, no history of MI	10	8	2
History or electrocardiographic evidence of MI	40	8	32
R–ST segment elevation	4	0	4
Left ventricular enlargement	25	3	22
Hemodynamic:			
Increased LVEDP (>12 mm Hg)	23	1	22
Reduced CI (<2.5 liters/min per m²)	12	1	11
Arteriographic:			
3 vessel disease	16	5	11
2 vessel disease	16	3	13
1 vessel disease	18	7	11

CI = cardiac index; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction.

TABLE II

Relation Between Zones of Asynergy in the Right (RAO) and Left (LAO) Anterior Oblique Views in 50 Patients with Simultaneous Biplane Ventriculograms

	LAO Ventriculogram			
RAO Ventriculogram	Normal	Abnormal (Asynergy)	Septal Asynergy	Posterolateral Asynergy
Normal (15)	15	0	...	...
Abnormal (asynergy) (35)	10	25	25	6
Anterior only (1)	1	0	...	...
Apical only (1)	1	0	...	...
Inferior only (5)	5	0	...	...
Mixed anterior-apical (8)	1	7	7	0
Mixed anterior-inferior (1)	1	0	...	...
Mixed anterior, apical, and inferior (19)	1	18	18	6

Determination of minor diameters, ventricular volumes and ejection fractions: Minor diameters in both the right and left anterior oblique silhouettes (DRAO and DLAO) were determined by direct measurement (Fig. 2) and by calculation (D = 4A/πL at end-diastole and end-systole) (Table III). There was agreement between minor diameters in the right and left anterior oblique projections (measured and calculated) in the normal subjects. In addition, the measured and calculated values in the *same* silhou-

TABLE III

Correlations Between Minor Diameters in the Right and Left Anterior Oblique Views (means ± standard error of the means)*

	End-Diastole		End-Systole		%ΔEnd-Diastole Minus End-Systole	
	DRAO	DLAO	DRAO	DLAO	DRAO	DLAO
Normal control subjects (10)						
Calculated	4.7 ± 0.3	4.7 ± 0.3	3.1 ± 0.3	3.2 ± 0.3	34 ± 2.5	32 ± 2.4
Measured	4.7 ± 0.3	4.8 ± 0.3	2.9 ± 0.2	3.1 ± 0.3	38 ± 2.6	35 ± 2.8
CAD without asynergy (15)						
Calculated	5.1 ± 0.1	5.5 ± 0.2	3.2 ± 0.1	3.6 ± 0.1	37 ± 2.6	34 ± 2.4
Measured	5.1 ± 0.1	5.2 ± 0.1	3.1 ± 0.1	3.4 ± 0.1	39 ± 2.8	35 ± 2.8
CAD with asynergy, total (35)						
Calculated	6.8 ± 0.2	7.2 ± 0.3	4.9 ± 0.2	5.4 ± 0.2	26 ± 2.8	25 ± 2.8
Measured	6.2 ± 0.2	6.6 ± 0.3	4.8 ± 0.2	5.3 ± 0.2	23 ± 2.9	20 ± 2.4
CAD with asynergy, normal-sized LV (13)						
Calculated	5.4 ± 0.3	6.0 ± 0.3	3.9 ± 0.2	4.5 ± 0.2	28 ± 2.9	25 ± 2.9
Measured	4.9 ± 0.3	5.5 ± 0.3	3.8 ± 0.2	4.3 ± 0.3	23 ± 2.8	20 ± 2.8

* Differences in values (DRAO vs. DLAO, calculated vs. measured) were not significant by paired *t* test.

CAD = coronary artery disease; D = diameter; DLAO and DRAO = minor diameters in the left and right anterior oblique views, respectively; normal-sized LV = end-diastolic volume less than 250 cc, as calculated by both biplane and single plane formulas.

ette agreed closely with one another. In patients with coronary artery disease these relations did not hold: (1) minor diameters in the right and left anterior projections were often several millimeters apart, whether these values were directly measured or calculated, with the left anterior oblique value usually larger. This difference was observed at end-diastole and end-systole in both small and large hearts in patients with and without visual evidence of ventricular asynergy. Although these differences existed, they were not statistically significant. (2) Similarly, the measured and calculated values in the *same* silhouette also differed by several millimeters, with the calculated values usually larger than the measured values. (3) The percent change from end-diastole to end-systole was nearly the same in both views, although patients with asynergy had lower absolute values.

The mean differences between minor diameters in the two projections in the control group were 0 and 1 mm at end-diastole and end-systole, respectively. Although these values were 4 and 5 mm, respectively, in patients with asynergy, the differences between the groups were not statistically significant.

End-diastolic and end-systolic ventricular volumes were determined by single plane and biplane formulas. In normal subjects there was close agreement between volumes determined by single and biplane techniques (Fig. 3A). More disparity was observed in patients with coronary artery disease (Fig. 3B), especially those with ventricular asynergy (Fig. 3C). Thus, although significant regression coefficients were present in patients with all three conditions, the widest confidence limits were observed in those with asynergy: The regression equation for patients with asynergy who had an end-diastolic volume of less than 250 ml was $Y = 0.7X + 60 \pm 32$ (standard error of estimate) compared to the overall group value of $Y = 0.8X + 65 \pm 60$.

Ejection fractions determined by biplane and single plane techniques were similar to each other in the normal subjects (68 percent ± 1.8 vs. 70 percent ±2.5) and in the patients with coronary artery disease (without asynergy 75 percent ± 1.3 vs. 78 percent ± 1.7, and with asynergy 47 percent ± 3.0 vs. 44 percent ± 3.3). Average differences were 0.04 in patients without asynergy and 0.08 in patients with asynergy. Nine of the 25 patients with normal wall motion had greater than 0.04 differences between single plane and biplane values. In eight of these nine patients, the ejection fraction in the right anterior oblique projection was larger than the biplane value. By contrast, 12 of the 20 patients with asynergy (and more than 0.08 difference between values for single plane and biplane ejection fractions) had larger biplane values. In these 12 patients there was more end-diastolic to end-systolic shortening in minor diameters in the left than in the right anterior oblique projection (27 ± 3.2 vs. 18 percent ± 2.6, $P < 0.001$).

Discussion

Discussion of the findings in this study focuses on two specific areas: (1) clinical, hemodynamic and arteriographic factors associated with ventricular asynergy, and (2) value of the left anterior oblique view in assessing wall motion and in calculating ventricular volumes and ejection fractions.

Asynergy and Related Findings

Seventy percent of the patients with coronary artery disease had angiographic evidence of left ventricular asynergy. This prevalence is similar to that reported by Bjork et al.[11] but greater than that re-

ported by Cheng.[12] The difference may be explained by the increased frequency of transmural myocardial infarction in our study. History of such an infarction or abnormal Q waves on the electrocardiogram, or both, are relatively specific indicators of asynergy, as is R–ST segment elevation (Table I).

Left ventricular enlargement in a multiview cardiac series is another useful finding. However, the absence of these findings did not necessarily correlate with normal wall motion in our study or those of others.[3,10,11] Thus, left ventricular asynergy was found in more than 50 percent of the patients with a normal chest roentgenogram and in 20 percent of those patients with a completely normal electrocardiogram and no history of infarction.

Hemodynamic abnormalities observed during catheterization were another relatively specific sign of abnormal wall motion. The reduced stroke output may result from derangements in myocardial fiber shortening caused by the altered configuration of the ventricle, with increased left ventricular end-diastolic pressure representing either a Starling effect or increased ventricular wall stiffness.[15] Although patients with asynergy tended to have multivessel disease, many patients with abnormal wall motion had only single vessel disease. The location of arterial lesions has been shown previously to correlate with sites of asynergy.[10] Asynergy was not observed in our series of 10 normal subjects.

The Left Anterior Oblique Projection

The left anterior oblique projection provides information about two zones of the left ventricular wall (septal and posterolateral) that are not visualized in the right anterior oblique view. These zones were not asynergic in the absence of corresponding involvement of the anterior, apical or inferior zones on the latter view (Table II). Thus, the prevalence of asynergy in a given series of patients will not be altered by the addition of the left anterior oblique view. Why there is often less asynergy in the posterolateral region is inadequately understood; the phenomenon may be due in part to the relatively reduced frequency of disease in the left circumflex artery. In previous studies[16–18] ventricular volumes calculated from biplane and single plane silhouettes correlated closely with one another, as did ejection fractions derived from these volumes. These studies did not comment on the presence of localized abnormalities of ventricular wall motion and the left and right anterior oblique projections were used in only one study.[16] A good correlation was observed between measured minor diameters in the two oblique views. Correlations have also been reported between calculated minor diameters in the anteroposterior and lateral views[17] and between volumes determined in the right anterior oblique and anteroposterior projections.[18]

In our study the minor (transverse) diameters in the right and left anterior oblique views were similar in normal subjects whether these values were measured or calculated. In patients with coronary artery

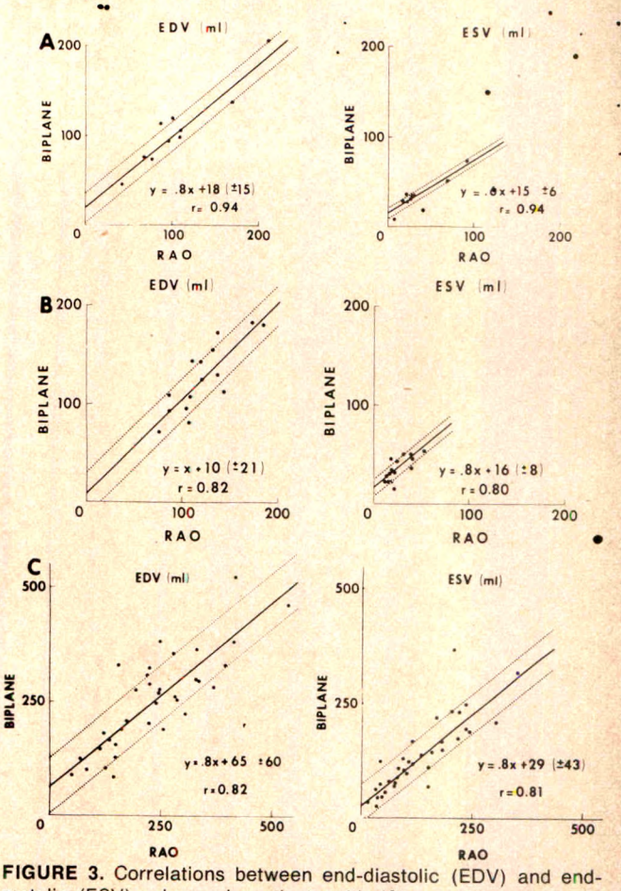

FIGURE 3. Correlations between end-diastolic (EDV) and end-systolic (ESV) volumes in patients with (**A**) normal coronary arteries and wall motion, (**B**) coronary artery disease but no visible asynergy, and (**C**) coronary artery disease and asynergy. In all three groups values for end-diastolic and end-systolic volumes were not significantly different whether biplane or right anterior oblique techniques were used; however, the greatest scatter is seen in patients with asynergy.

disease, calculated values often exceeded measured ones and diameters in the left anterior projection were often larger than the corresponding diameters in the right anterior oblique projection at both end-diastole and end-systole. This was especially true in patients with asynergy and was found in both small and large hearts. The reasons for this disparity in some patients without visible asynergy are not apparent. It is possible that subtle segmental changes in the ventricular wall have made these ventricles less symmetrical. Because the minor diameters in the right and left anterior oblique views are perpendicular to each other in the same plane (unlike those in the anteroposterior and lateral views), asymmetry in cross section is more likely to be detected by this technique, which uses a vertical and horizontal minor diameter. In addition, the left anterior oblique projection is more likely to cause small errors in this type of determination because the view is from the apex of the ventricle rather than perpendicular to the long axis, and tilting in one direction or another may distort the areas and diameters. In patients with visible asynergy, the disparity between calcu-

lated and measured diameters reflects the irregular shape of these ventricles, especially at end-systole. Differences at end-diastole may be caused by asymmetry due to abnormalities of ventricular relaxation.

Since these diameters represent an important factor in the volume equation, it was not surprising to find that the greatest difference between volumes determined in the right anterior oblique and biplane views occurred in patients with asynergy. Even when patients with large ventricles are omitted, the confidence limits of the regression equation are very wide. Thus, a patient with asynergy and an end-diastolic volume of 100 ml by the right anterior oblique calculation might have a corresponding calculated biplane end-diastolic volume ranging from 85 to 205 ml (using ±1 standard deviation of the regression formula), whereas a patient without asynergy would have a biplane volume ranging from 83 to 113 ml. (Since there is no in vivo technique for accurately measuring true ventricular volume, we made no attempt to indicate which technique most closely approximates true volume.)

Ejection fractions determined by methods using the biplane and right anterior oblique views tended to be similar to each other in patients with and without asynergy. The average differences were 0.04 in patients without asynergy and 0.08 in patients with asynergy. When values in individual patients demonstrated greater than average differences, patients without asynergy tended to have larger values in the right anterior oblique projection. (This may reflect technical problems in drawing outer borders of papillary muscles in vigorously contracting ventricles.) By contrast, patients with asynergy tended to have larger biplane values. In these latter patients, shortening in the minor axis in the left anterior oblique view was significantly greater than shortening in the minor axis in the right anterior oblique view. These findings agree with the visual observations that wall motion in the left anterior oblique view is often better than that in the right anterior oblique view when asynergy is present (Table II).

Conclusions

Because biplane ventriculography in the right and left anterior oblique projections provides angiographic documentation of left ventricular wall motion in *all* five zones, it is a useful adjunct in evaluating ventricular asynergy and function. Ventriculograms can be obtained simultaneously or in sequence, with the former method preferred to avoid effects of contrast agent on ventricular function. When both simultaneous biplane and single plane facilities are available, the biplane facility is most efficiently used in patients whose clinical findings suggest asynergy. Such patients often have left ventricular enlargement on chest roentgenogram and historical or electrocardiographic evidence of a prior myocardial infarction. In addition, they may have hemodynamic abnormalities, particularly increased left ventricular end-diastolic pressure. Previous studies have shown a correlation between increased ventricular diastolic pressures, ventricular asynergy and diastolic filling waves and sounds (third or fourth heart sounds, or both).[5,19] Thus, patients with diastolic heart sounds, left ventricular enlargement and prior myocardial infarction are optimal candidates for biplane ventriculography.

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Devolutionary Pattern of Coronary Atherosclerosis in Patients with Angina Pectoris

Coronary Arteriographic Studies

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The devolutionary pattern of coronary atherosclerosis in patients with angina pectoris was studied in 47 persons cinearteriographically. Two subsets of patients were identified at the initial examination. The first comprised 12 patients who did not have coronary atherosclerosis. In these 12, the cinearteriographic findings remained normal on repeated study 15 to 73 months later. The second subset included 35 patients with severe obstructive coronary atherosclerosis. When coronary visualization was repeated 15 months later, arterial disease remained stable in 11 patients (31.4 percent). Significant progression of the arterial disease was observed in the remaining 24 patients (68.5 percent). The frequency of hyperlipidemia, clinical diabetes, systolic and diastolic hypertension and a positive family history of coronary heart disease was not significantly different in those with stable and progressive disease. Furthermore, the distribution of the initial disease did not distinguish one group from the other. Since collateral channels were more prolific in patients who ultimately were classified as having stable arterial disease, it is possible that the initial severity of disease in this group was greater than in those with progressive disease. None in the latter group noted a reduction in the frequency or severity of angina pectoris. One third of those with stable disease did record such a reduction. However, paradoxically, two patients with stable coronary disease had a new myocardial infarction in the interval between examinations.

Our findings suggest that the devolutionary pattern of coronary atherosclerosis in patients with angina pectoris as observed cinearteriographically is unpredictable and apparently unrelated to commonly cited risk factors. They indicate that the severity of angina pectoris is the most precise guide to progressive coronary artery disease even though progressive disease can occur without affecting angina. The occurrence of myocardial infarction in patients with stable disease underscores the fact that many determinants influencing myocardial perfusion are not identified by cinearteriography.

Although coronary atherosclerosis progresses inexorably, the actual devolutionary pattern of the arterial disease in symptomatic patients is obscure. Additional information on this subject, obtained by repeated visualization of the coronary circulation in patients with angina pectoris, forms the basis of our report.

Material and Methods

The study group comprised 47 patients, 36 men and 11 women, ranging in age from 33 to 65 years (mean 48.6 years). No patient had undergone saphenous vein bypass surgery for coronary heart disease.

Clinical data on each subject included a record of risk factors for coronary atherosclerosis—namely, hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, stressful life pattern and physical indolence as

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TABLE I

Age Distribution, Sex and Interval Between Studies in the Different Groups

Group	Patients (no.)	Sex M	Sex F	Mean Age (yr)	Mean Interval Between Studies (mo)
NCAD	12	6	6	46.7	32.9
CAD	35	31	4	49.6	26.2
SCAD	11	10	1	50.2	20
PCAD	24	21	3	49.2	25.8

CAD = coronary artery disease; NCAD = no coronary artery disease, PCAD = progressive coronary artery disease; SCAD = stable coronary artery disease.

well as the onset, frequency and severity of angina pectoris and details of electrocardiographic abnormalities. Severity of angina pectoris was classified from grade 1 to 3. Each item was reappraised before coronary visualization was repeated.

Coronary arteriography was performed according to the Sones technique utilizing a 6-inch image tube and 35 mm cine film. Obstructing atherosclerosis was estimated as percent of the lumen of the involved vessel. Myocardial contractility was evaluated by ventriculography.

Progression of coronary artery disease was considered significant when obstruction increased 20 percent or more in any single vessel or when an artery became completely occluded.

Results

At the time of initial arteriography, 12 of the 47 patients were observed to have normally patent coronary vessels (Table I). These 12 were classified as having no coronary artery disease. Six patients were men and six were women. Their ages ranged from 33 to 60 years (mean 46.7 years). A positive family history of coronary heart disease was recorded in 5 of these patients (41.6 percent). An equal number had cholesterol values greater than 250 mg/100 ml. None had hypertension or diabetes mellitus (Table II). Angina pectoris was classified as grade 1 or 2 in six subjects and grade 3 in the remaining six patients. Without exception, the electrocardiographic findings were abnormal; however, the results of left ventriculography were uniformly normal.

The remaining 35 patients, 31 of whom were men, had obstructing coronary atherosclerosis and were classified as having coronary artery disease. Their ages ranged from 36 to 65 years (mean 49.6 years) (Table I).

A positive family history of coronary heart disease was obtained in 21 patients in this group (60 percent). Cholesterol values exceeded 250 mg/100 ml in 25 subjects (71.4 percent). Chemical diabetes mellitus was present in 7 persons (20 percent). Abnormal elevations of systolic and diastolic blood pressure levels were observed in six patients (17.1 percent) (Table II). Angina pectoris was classified as grade 1 in three patients (8.5 percent), grade 2 in 22 (62.5 percent) and grade 3 in 10 (28.5 percent).

Only two of the patients in the group with coronary artery disease had single vessel disease (5.5 percent). Five subjects had double vessel disease (14.2 percent), and 28 had triple vessel disease (80 percent). The right coronary vessel was involved in 31 cases (88.5 percent), the left anterior descending coronary artery in 32 (91.4 percent) and the left circumflex artery in 31 (88.5 percent) (Table III). Collateral blood vessels were observed in 17 patients (48.5 percent).

Left ventriculography was performed at the time of each arteriographic study in 25 of the patients with coronary artery disease. During the initial study, myocardial contractility was considered significantly impaired in 15 of these subjects (60 percent).

Group Without Coronary Artery Disease

The interval between cinearteriograms in this group ranged from 15 to 73 months (mean 32.9 months) (Table I). In that interval the severity of angina remained unchanged in six patients (50 percent), decreased in three (25 percent) and increased in the remainder. Without exception, the electrocar-

TABLE II

Risk Factors

	NCAD (12 patients)		CAD					
			Total (35 patients)		SCAD (11 patients)		PCAD (24 patients)	
Risk Factors	no.	%	no.	%	no.	%	no.	%
Family history of CAD	5	41.6	21	60	8	77.7	13	54.1
Serum cholesterol	5	41.6	25	71.4	8	77.7	17	70.8
Diabetes mellitus	...	...	7	20	2	18.1	5	20.8
Hypertension	...	...	6	17.1	2	18.1	4	16.7

Abbreviations as in Table I.

TABLE III

Comparison of Arterial Involvement in Patients with Stable and Progressive Coronary Artery Disease

	Stable Disease		Progressive Disease			
			Initial Study		Repeat Study	
Artery	Involved	Occluded	Involved	Occluded	Progressed	Occluded
LAD	11	3	21	2	9	5
LCA	10	...	21	1	15	5
RCA	9	5	22	5	8	6

LAD = left anterior descending coronary artery; LCA = left circumflex coronary artery; RCA = right coronary artery.

diograms remained stable. The second radiologic examination reaffirmed the presence of normal coronary arteries and myocardial contractility in every member of this group.

Group With Coronary Artery Disease

The interval between examinations in this group ranged from 8 to 50 months (mean 26.2 months) (Table I). In 11 of the 35 patients, the degree of coronary artery disease was unchanged (31.4 percent). These patients were classified as having stable coronary artery disease. A significant increase in the degree of arterial obstruction was observed in 24 patients (68.5 percent). These patients were therefore considered to have progressive coronary artery disease.

Group with stable coronary artery disease: Of the 11 patients in this category, 10 were men. Ages ranged from 40 to 58 years (mean 50.2 years). The interval between arteriograms ranged from 8 to 41 months (mean 20 months) (Table I).

A positive family history for coronary heart disease was presented by eight patients (77.7 percent). Serum cholesterol values exceeding 250 mg/100 ml were recorded in an equal number. Chemical diabetes mellitus and elevated levels of systolic and diastolic pressure were each discovered in two patients (18.1 percent) (Table II).

Angina pectoris was classified as grade 2 in seven patients (63.6 percent) and grade 3 in four patients (36.3 per cent) at the time of initial coronary visualization. When the second examination was performed, angina had decreased in approximately one third of the group, increased in one third and was unchanged in the remaining patients.

Evidence of a transmural myocardial infarction was present in two patients (18.1 percent) when the first examination was performed and developed in two additional patients before the second examination. In the remaining seven subjects (63.6 percent) the electrocardiogram remained unchanged.

All of the patients in the group with stable coronary artery disease had atherosclerotic involvement of left anterior descending coronary artery (Table III). In three subjects the vessel was completely occluded (27.2 percent). The left circumflex artery was involved but not completely obstructed in 10 patients (90.9 percent) (Table III). The right coronary artery was diseased in nine patients (81.8 percent) and completely occluded in five of them (55.5 percent) (Table III). Collateral vessels were present in eight patients (72.7 percent) initially and in one additional patient at the time arteriography was repeated (Fig. 1).

Left ventriculography was performed in both studies in only seven patients of this group (63.6 percent). Impaired myocardial contractility was observed in four patients (57.2 percent) initially and was not diagnosed in any additional patients during the second examination.

Group with progressive coronary artery disease: Of the 24 patients included in this group, 21 were men. Their ages ranged from 36 to 65 years (mean 49.2 years). The interval between the arteriographic studies was 11 to 50 months (mean 25.8 months) (Table I).

A positive family history of coronary heart disease was obtained in 13 patients (54.1 percent). Cholesterol levels exceeded 250 mg/100 ml in 17 patients (70.8 percent); chemical diabetes was noted in 5 (20.8 percent) and elevated levels of systolic and diastolic pressure in 4 (16.7 percent) (Table II). At the time of the initial examination, angina pectoris was considered grade 1 in 3 patients, grade 2 in 15 and grade 3 in 6. On repeat arteriographic study, angina had become significantly worse in half of the group; in no instance did it become less severe.

Electrocardiographic indications of a transmural myocardial infarction were present in 8 patients at the time of the initial arteriography (33.3 percent) and in 10 patients (41.6 percent) when the second examination was performed. However, new transmural infarctions were observed in two patients without previous infarction. Thus, four separate instances of myocardial infarction are believed to have taken place between examinations.

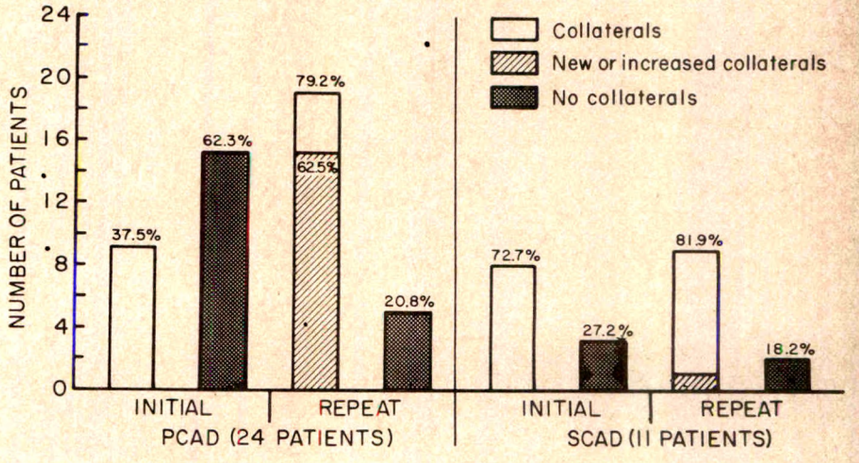

FIGURE 1. Comparison of collateral circulation in the two subgroups of patients with coronary artery disease. PCAD and SCAD = progressive and stable coronary artery disease, respectively.

Initially, the right coronary artery was involved in 22 patients (91.2 percent) and the left anterior descending and left circumflex arteries in 21 subjects each (87.5 percent) (Table III). The right coronary artery was occluded in 5 patients and the left anterior descending artery in 3. Collateral channels were seen in nine patients (37.5 percent) (Fig. 1). Results of left ventriculography were abnormal in 11 of the 18 patients examined (61.2 percent).

Significant progression of disease in the right coronary artery was observed in eight patients (33.3 percent), and complete occlusion was seen in six of these eight. Marked worsening of lesions in the left anterior descending coronary artery was noted in nine subjects (37.5 percent) and resulted in complete occlusion of the artery in five. Progressive involvement of the left circumflex artery was observed in 15 patients (62.5 percent); complete occlusion developed in 5 of these 15. At the time of the second cinearteriographic study, collateral vessels were observed in 19 patients (79.2 percent) (Fig. 1). The left ventriculogram was believed indicative of myocardial dysfunction in 15 subjects (83.3 percent).

Discussion

At the outset of this cinearteriographic study, two subsets of patients with angina pectoris were identified. The hallmark of the first was a normal coronary arteriogram. Subjects with angina and normally patent coronary arteries have been previously described by a number of investigators.[1–8] Accumulated experiences have not yet provided a satisfactory explanation for the chest discomfort simulating ischemic heart disease. Prognosis, like cause, has not been defined. Although some patients have died, most long-term experiences suggest a benign fate. The observations recorded in our survey indicate that coronary arteriograms remain normal although angina pectoris usually persists.

The second subset comprised patients with obstructive coronary atherosclerosis. Approximately 95 percent of these subjects had double or triple vessel disease. Each of the major arteries was equally vulnerable. Homocoronary or intercoronary collateral vessels were visualized in almost half of the patients.

When cinearteriography was repeated approximately 1 to 4 years after the initial examination, significant progression in the arterial obstruction was observed in more than two thirds of the patients included in this group. This frequency of progression is somewhat higher than that recorded by others.[9]

Is it possible to predict progression of coronary artery disease?: Even in retrospect, it is not possible to predict who among the second subset was more likely to have stable or progressive coronary artery disease. The distribution of the initial abnormality does not appear to be a clue since it was remarkably similar in both groups at the outset. However, since collateral channels initially were more prolific in the group with stable disease, more severe obstructions that could not worsen materially may have been more common in these patients. The incidence of risk factors including a positive family history for coronary heart disease, hyperlipidemia, clinical diabetes mellitus and systolic and diastolic hypertension was not higher in the patients with progressive disease and cannot be held responsible for the more rapid increase in arterial atherosclerosis. The mean interval between examinations was somewhat longer for the group with progressive disease, but it is unlikely that this single factor accounts for the differences observed cinearteriographically. From the items available for study, it is reasonable to conclude that it is not possible to predict among patients with angina pectoris the pace at which the arterial disease will worsen.

In observing the cinearteriographic depiction of the devolutionary pattern of coronary atherosclerosis, lesions in the left circumflex artery appeared to mature more rapidly than others. However, complete occlusions developed more frequently in the left anterior descending and right coronary arteries.

New collateral vessels were noted in almost two thirds of patients with progressive but in none of those with stable disease, thus emphasizing the role of progressive arterial disease as the primary stimulus for the development of these channels.[10–15] The protective role of collateral vessels is supported by the observation that none of the subjects with progressive disease who had collateral vessels at the first examination had abnormal myocardial contractility even when complete occlusion of a major artery occurred subsequently.

Severity of angina pectoris: The degree of severity of angina pectoris appeared to be a crude guide to the progress of the arterial disease. One third of the patients with stable coronary disease noted a reduction in the frequency and severity of angina in the interval between arterial visualizations. No one with progressive coronary disease had a reduction in severity of angina and in half of the group the severity had significantly increased. Paradoxically, two patients with stable coronary artery disease had a new myocardial infarction in the interval between examinations.

Clinical implications: Limited conclusions are warranted from this study. The devolutionary pattern of coronary atherosclerosis in patients with angina pectoris as seen cinearteriographically is quite unpredictable, apparently unrelated to risk factors and essentially unheralded by specific clinical manifestations separating those with rapidly progressive disease from those with relatively stable lesions. These observations stress the gap that, in the present state of knowledge, separates anatomic structure from function, and they underscore the many determinants regulating the balance between coronary perfusion and myocardial metabolism that fall beyond the scope of cinearteriography.

Acknowledgment

We thank Ms. Barbara Podliski for her efforts in preparation of this manuscript.

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Effects of Factors Predisposing to Atherosclerosis on Formation of Coronary Collateral Vessels

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Two hundred eighteen consecutive patients undergoing selective coronary angiography were studied to determine the effects of underlying predisposing coronary risk factors on the formation of intercoronary collateral anastomoses. The presence or absence of hyperlipoproteinemia, diabetes mellitus, glucose intolerance, hypertension or obesity did not influence the formation of these intercoronary collateral channels. Our findings suggest that there are presently no measurable clinical factors that permit prediction of the presence of coronary collateral channels in an individual patient. Factors predisposing to atherosclerosis have a similar distribution in patients with and without such vessels.

With the advent of techniques capable of demonstrating interarterial coronary anastomosis, several important postmortem and in vivo studies in man have been reported.[1-5] These studies clearly demonstrate that the most important factor in determining the presence of functionally significant collateral vessels is the severity of the coronary arterial stenosis. The presence of these vessels also appears to be related to the presence of myocardial ischemia as demonstrated by abnormal postexercise electrocardiograms and abnormal transmyocardial lactate production.[6] It is generally accepted that coronary collateral vessels are congenitally determined potential channels that function only in response to (1) a pressure difference across or between coronary arteries as a result of obstruction, or (2) myocardial ischemia distal to the obstruction.[7] The response to myocardial ischemia might explain the greater prevalence of these vessels in patients with anemia and arterial unsaturation as reported by Zoll et al.[1] However, the presence of both severe arterial obstruction and evidence of myocardial ischemia in some patients without collateral vessels suggests that additional factors may promote or inhibit collateral development. This report describes a study of the relation between factors predisposing to coronary atherosclerosis and the presence of collateral vessels in patients with documented coronary atherosclerosis.

Material and Methods

Case Material

Two hundred eighteen consecutive patients undergoing selective coronary cinearteriography were studied. In all cases arteriography was performed to evaluate angina pectoris or chest pain of obscure cause or to assess coronary circulation in patients being considered for cardiac valvular surgery. Thus, the group represents some degree of preselection rather than a random sampling of the population at large. One hundred sixty-four patients were male, and 54 were female; the age range was 29 to 69 years (mean 47 years).

Symptoms: The clinical records of all patients in the study were reviewed. At least one of us had assumed primary responsibility for the care of each patient during the current hospitalization. The criteria for the diag-

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nosis of angina pectoris and for myocardial infarction were those of the New York Heart Association, Committee on Nomenclature.[8]

Angiography: The degree of coronary atherosclerosis was assessed by selective cineangiography performed at a rate of 60 frames/sec. The angiograms were taken in multiple projections and in many instances after sublingual administration of nitroglycerin. Kemp et al.[9] have shown that this technique accurately defines the degree of disease in vessels up to a size of 300 μ. The angiograms were reviewed independently by two of us and were judged to be of high diagnostic quality in each case. Each patient also underwent diagnostic left and right heart catheterization and cineventriculography.

The degree of atherosclerosis was rated as follows: 0 (indicating no discernible luminal narrowing or irregularity), 50 percent narrowing or less, 75 percent narrowing, or 90 percent narrowing or greater (the latter indicating severe segmental narrowing or complete occlusion of the vessel).

Criteria for the presence of coronary collateral vessels were as previously reported[5]: (1) direct visualization of accessory blood vessels either filling the distal segment of an occluded or severely stenotic artery, or subserving the area of myocardium that would ordinarily be supplied by the severely stenotic vessel; and (2) visualization of a coronary artery after injection of contrast material into the contralateral vessel.

Lactate metabolism: Paired blood samples for lactate determinations were obtained from an indwelling arterial catheter and a second catheter fluoroscopically positioned within the coronary sinus. Measurements were made "at rest" and again during stress to the oxygen delivering systems induced by infusion of isoproterenol.[10] Lactate was analyzed in duplicate,[11] and a gross production of lactate was considered to be abnormal.[12]

Coronary Risk Factors

Lipid determinations: Plasma samples were drawn from each patient after a 12 to 16 hour overnight fast and were shipped at 4° centigrade to the Molecular Disease Branch of the National Heart and Lung Institute for analysis as previously reported.[13] The plasma was analyzed for total cholesterol[14] and triglycerides,[15] and the lipoprotein was fractionated into very low density lipoprotein, high density and low density components and determined in terms of lipoprotein cholesterol by a combination of ultracentrifugation and precipitation procedures.[16] The normal limits of plasma cholesterol and triglyceride and low density lipoprotein cholesterol previously described[16] were used in part to define the hyperlipoproteinemic states. Type II hyperlipoproteinemia was established by the finding of a low density lipoprotein cholesterol value greater than the age-adjusted 95 percentile limit, and type IV by the finding of a pure endogenous hypertriglyceridemia (prebeta lipoproteinemia) with a plasma triglyceride value greater than the age-adjusted 95 percentile limit.[16]

Carbohydrate tolerance: An intravenous glucose tolerance test was performed in all but 16 patients who had clinically overt diabetes mellitus. After an overnight fast, 0.5 g/kg of glucose was infused rapidly and plasma samples were drawn every 10 minutes for 1 hour. The rate of glucose disappearance in percent per minute (IVGTT k) was calculated, and a value of less than 1.0 was considered abnormal.

Hypertension: Hypertension was defined as diastolic blood pressure greater than 90 mm Hg recorded (1) on two separate occasions during the present hospitalization, (2) on at least two previous occasions by a physician, or (3) at the time of cardiac catheterization.

Obesity: Obesity was defined as a body weight 20 percent greater than medium ideal weight according to Metropolitan Life Insurance Company tables.[17]

TABLE I

Relation Between Frequency of Collateral Channels and Severity of Vessel Disease

Degree of Arterial Narrowing	RCA Patients (no.)	RCA With Collateral Channels no.	RCA With Collateral Channels %	LAD and/or LCF Patients (no.)	LAD and/or LCF With Collateral Channels no.	LAD and/or LCF With Collateral Channels %
0	139	0	0	144	0	0
50%	11	1	9.1	7	0	0
75%	8	1	12.5	16	1	6.2
≥90% (or total occlusion)	60	51	85.0	51	42	82.4

LAD = left anterior descending branch of left coronary artery; LCF = left circumflex branch; RCA = right coronary artery.

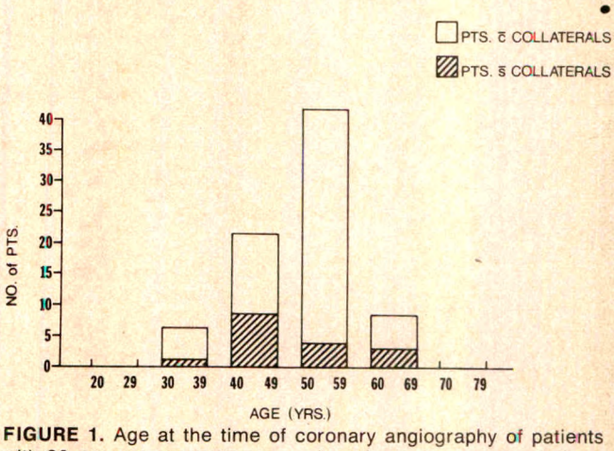

FIGURE 1. Age at the time of coronary angiography of patients with 90 percent or greater narrowing of a major coronary artery. There was no statistical difference between the groups with and without collateral vessels.

Results

For analysis of collateral vessels, the right and left coronary arterial systems were considered independently (Table I). No collateral vessels were visualized in any patient with less than 50 percent narrowing of either coronary arterial system. Intercoronary anastomoses were seen in 1 of 18 vessels with 50 percent narrowing and in 2 of 24 with 75 percent narrowing. However, in 93 of 111 vessels with 90 percent narrowing or greater, collateral channels were present and filled the distal portion of the vessel beyond the obstruction. There were no significant lesions of the main left coronary artery.

Since the stimulus for collateral vessel formation, as defined by these methods, appeared to be the presence of severe obstruction of a vessel, compari-

son was made between patients with 90 percent or greater narrowing of the coronary artery *with* collateral vessels and patients with 90 percent narrowing or greater *without* collateral vessels. Fifteen patients had severe obstruction of both the right coronary and the left anterior descending arterial systems; and all 15 had collateral channels supplying both vessels. Of 81 patients with severe single vessel disease, 65 had collateral channels and 16 did not. There were, therefore, 80 patients with significant narrowing of one or two vessels and collateral channels and 16 patients with severe obstruction and no collateral channels. These 96 patients are the basis for the remainder of the study. There was no significant difference in the age of patients with and without collateral vessels at the time of study (Fig. 1).

Symptoms: Angina pectoris was the presenting complaint in all but 2 of the 96 patients. The other two patients had hemodynamically significant aortic stenosis and both had coronary collateral vessels (Table II). There was no statistical difference between patients with and without collateral vessels in regard to the initial symptom of the coronary artery disease or history of previous acute myocardial infarction.

TABLE II

Frequency of Clinical Abnormalities in Patients With and Without Collateral Channels

	Collateral Channels		
	Present (80 patients)	Absent (16 patients)	*P* Value
Angina pectoris	78 (97%)	16 (100%)	NS
History of infarction	44 (55%)	6 (38%)	NS
Initial symptom			
Angina	61 (76%)	13 (81%)	NS
Infarction	17 (21%)	2 (12%)	NS

NS = not significant; *P* = probability.

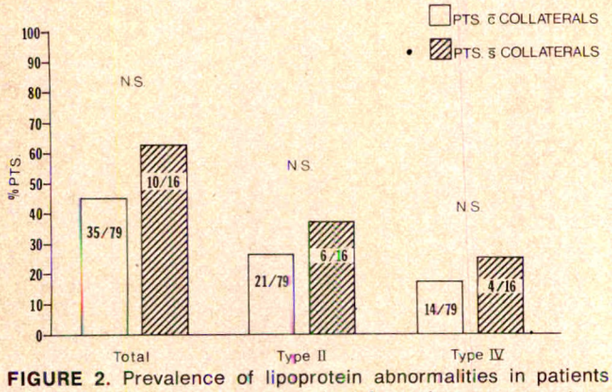

FIGURE 2. Prevalence of lipoprotein abnormalities in patients with 90 percent or greater narrowing of a major coronary artery. The presence of a lipoprotein abnormality did not influence the occurrence of collaterals. N.S. = not significant.

Lipoprotein abnormalities: Figure 2 shows the distribution of abnormal lipoprotein patterns in patients with and without collateral vessels. One patient with visible intercoronary collateral channels did not have adequate lipoprotein studies and is not included in this evaluation. Thirty-five of 79 patients with collateral vessels and 10 of the 16 patients without such vessels had a lipoprotein abnormality; this difference was not statistically significant. Of the five types of lipoprotein abnormality identified by Frederickson, only the type II and the type IV abnormalities occurred in this series. Figure 2 also shows the distribution of these two lipoprotein abnormalities in the patients with and without collateral vessels. There was no significant difference between the groups.

Glucose intolerance: Figure 3 shows the distribution of overt diabetes mellitus or glucose intolerance in the patients with and without collateral vessels. Forty-nine of the 80 patients with collateral vessels and 12 of the 16 without collateral vessels demonstrated this metabolic abnormality. This difference was not statistically significant.

Hypertension and obesity: Figure 3 also shows the frequency of hypertension and obesity in the two

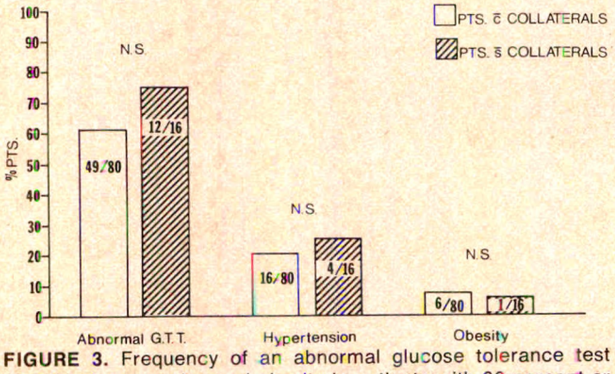

FIGURE 3. Frequency of an abnormal glucose tolerance test (G.T.T.), hypertension and obesity in patients with 90 percent or greater narrowing of a major coronary artery. These factors did not influence the occurrence of collateral vessels.

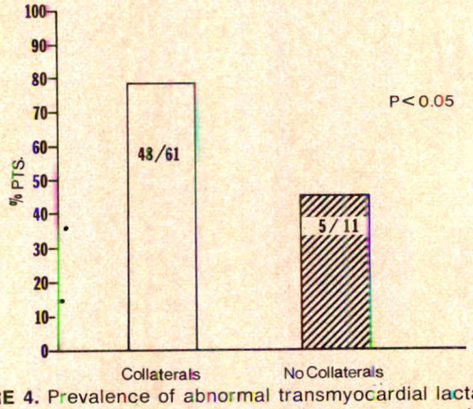

FIGURE 4. Prevalence of abnormal transmyocardial lactate production in patients with 90 percent or greater narrowing of a major coronary artery. This abnormality occurred more frequently in the group with collateral vessels than in the group without these vessels.

groups of patients. There were no differences between the groups, in regard to the presence of increased diastolic blood pressure or obesity. Since the number of patients with obesity was quite small, statistical analysis of group comparison may not be meaningful for this variable.

Lactate metabolism: Transmyocardial lactate studies were completed in 72 of the 96 patients with severe obstruction of the coronary arteries. The prevalence of abnormal lactate extraction was significantly greater in the patients with collateral vessels than in those without such vessels (Fig. 4).

Discussion

The analysis in this unselected group of patients with symptomatic documented coronary artery disease indicates that the formation of intercoronary collaterals is not affected by the presence of lipoprotein abnormalities, glucose intolerance, diastolic hypertension or obesity. Although glucose intolerance and hypertension are known to have effects on the vascular tree, these underlying abnormalities did not inhibit the formation of coronary collateral vessels. This finding is not completely unexpected since hypertension and diabetes mellitus have effects on small arteries (especially intramyocardial vessels) and perhaps even smaller vessels, but the collateral channels usually represent large epicardial vessels that do not appear to be influenced by these two factors.

A previous report from this laboratory[13] concluded that the atherosclerotic pattern of the coronary artery as demonstrated by selective coronary angiography was similar regardless of the underlying factor predisposing to formation of the atherosclerosis. The frequency of single and multiple vessel disease, isolated stenosis and multiple narrowings of the same vessel, long areas of narrowing and complete obstruction were not different in the groups with lipoprotein abnormalities, glucose intolerance, hypertension or obesity. These factors thus appear to be important only in creating susceptibility to development of coronary atherosclerosis; they apparently do not directly influence the anatomic location of the obstructive lesions or affect the opening of intercoronary connections.

This study of consecutive patients confirms the observation that the presence of severe coronary arterial stenosis is extremely important in the formation of functionally significant intercoronary anastomosis. Although anemia and arterial unsaturation may contribute to the formation of collateral vessels,[1] the presence of coronary atherosclerosis is clearly the most significantly finding in patients with these vessels. We believe that ischemia causes local vasodilatation which then causes a reduction in distal coronary arterial pressure; this reduction accentuates the gradient across the obstruction in a manner that sets the stage for enlargement of preexisting collateral channels. The increased frequency of lactate production under stress supports this concept.

It is possible that, in the patients without collateral vessels, the severity of the arterial lesion was "overread" and that the narrowing was actually less than 90 percent. However, 7 of the 16 patients had complete occlusion of the coronary artery, and this type of lesion is not easily misinterpreted. In addition, all patients had angina pectoris, and six had evidence of previous myocardial infarction. These two clinical features were also found in the group with collateral vessels.

The clinical findings and assessment of myocardial metabolism under stress to the oxygen delivery system were included in our study to show that our patients were not different from those in previously reported series. A prior history of angina pectoris or myocardial infarction could not be used to predict the presence of coronary collateral vessels. The greater frequency of lactate production by the myocardium under stress demonstrates that the coronary collateral channels do not necessarily protect a person from myocardial ischemia. However, the value of these channels in the general population is completely unknown, and the data available are from patients who have been studied mainly because they have symptoms of myocardial ischemia.

A shortcoming of our study is its comparison of data in a large group of patients with collateral channels with findings in a much smaller group without such channels. However, in a consecutive clinical study in which the anatomic appearance of atherosclerosis cannot be predicted, disparity in the size of the groups is unavoidable and not surprising. In spite of this disparity, our study has value as a consecutive study of patients who were not preselected except for the original indication for arteriography. Our findings indicate that the formation of coronary collateral vessels in patients with symptomatic coronary artery disease does not seem to be influenced by some of the major factors predisposing to the development of atherosclerosis.

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Hemodynamic Observations in Patients with Unstable Angina Pectoris

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Brachial and pulmonary arterial pressures were monitored for 48 hours in 26 patients with unstable angina pectoris and documented occlusive coronary artery disease. The circulatory response during 56 episodes of spontaneous anginal pain permitted the division of responses into three distinctive hemodynamic subsets. Patients in group I had an increased heart rate only with the spontaneous attack of angina; patients in group II had associated increases in brachial arterial pressure and slight increases in heart rate during the episodes of pain; patients in group III demonstrated increases in both brachial and pulmonary arterial diastolic pressures with minimal changes in heart rate. Resting hemodynamic data during pain-free periods were normal in 25 of 26 patients. Patients in all groups who had more than one episode of pain had similar hemodynamic responses to the first and later episodes. Although myocardial hypoxemia appears to be responsible for the spontaneous attack of angina, the hemodynamic responses to the attack varied but were highly specific for any one patient.

Our observations suggest that there may be various pathogenic mechanisms for "spontaneous" or resting angina in patients with occlusive coronary artery disease but that the mechanism and associated hemodynamic changes may be specific for individual patients.

The widespread application of aortocoronary artery saphenous vein bypass surgery for the relief of angina pectoris has resulted in a renewed interest in the hemodynamic alterations accompanying anginal attacks. A number of techniques, including drug administration,[1] right atrial pacing[2,3] and exercise,[4] have been used to induce angina and permit monitoring of the accompanying hemodynamic changes. More sophisticated analyses of left ventricular function, including examination of changes in compliance occurring with myocardial infarction[5] and angina,[6] have expanded understanding of altered left ventricular function. However, little attention has been focused on the hemodynamics of the spontaneous or apparently unprovoked anginal attack. This report presents the results of hemodynamic study during 56 episodes of spontaneous angina in 26 consecutive patients hospitalized with unstable or "preinfarction" angina.

Materials and Methods

Patients: Twenty-six patients admitted to Stanford University Hospital were accepted for this study of unstable angina on the basis of the following criteria:

1. History of one or more episodes of ischemic cardiac pain judged clinically severe enough to warrant admission to the coronary care unit because of suspected impending myocardial infarction.

2. Admission electrocardiograms with Q waves diagnostic of prior myocardial infarction by World Health Organization criteria, or depressed S-T segments with pain typical of myocardial ischemia. Although S-T segment

From the Cardiology Division, Stanford University School of Medicine, Stanford, Calif. This study was supported in part by National Institutes of Health Grants HL-5709 and HL-5866 and Contract 71-2482 from the Myocardial Infarction Research Unit, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. Manuscript accepted July 11, 1973.

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TABLE I

Clinical Profile of 26 Patients

Age (yr)	52.2 (average); 36–67 (range)
Sex	24 men, 2 women
Duration of angina (yr)	2.4 (mean); 1 day–20 years (range)
Duration of crescendo angina (mo)	<1 (25 patients)
Prior myocardial infarction	Present (10 patients); absent (16 patients)
Abnormal electrocardiogram	Present (26 patients)

elevation with pain typical of Prinzmetal's angina would not have excluded a subject from the study, such changes were not noted in our patient population.

•3. Initial values for serum enzymes (lactic dehydrogenase [LDH] and serum glutamic oxaloacetic transaminase [SGOT]) were within normal limits. Elevations of serum creatinine phosphokinase (CPK) levels to 100 international units/liter did not exclude a patient from the study.

4. Subsequent documentation by coronary arteriography of occlusive coronary disease with greater than 70 percent narrowing in at least one major coronary artery.

Each patient was seen by one of us on the day of admission and formally admitted to the study on the basis of clinical findings. The purposes of the study were explained to the patients, and their informed consent was obtained.

Protocol: The following protocol was carried out in each case: 1. Initial instrumentation was performed on admission. A catheter was positioned in the pulmonary artery to record both pulmonary arterial and pulmonary arterial wedge pressures. The Swan-Ganz thermodilution catheter was used in some cases. A 50 gauge, short polyethylene catheter was inserted into the brachial artery percutaneously. Both catheters were attached to Microdot transducers and Hewlett-Packard pressure preamplifiers. A Honeywell strip-chart recorder was utilized to record all the hemodynamic measurements. Early in the series in 11 patients the left ventricle was catheterized and pressure measured with the use of a no. 7F Cook catheter, which was then replaced by the short polyethylene catheter inserted in the brachial artery for continuous monitoring. Both brachial and pulmonary arterial pressures were recorded at least hourly and during any episode of chest pain at a paper speed of 25 mm/sec. Patients were carefully instructed to call the coronary care unit nurse immediately during any episode of substernal discomfort. During pain-free periods, the brachial arterial catheter was used for continuous pressure recording at a paper speed of 0.25 mm/sec. The pulmonary arterial catheter was not kept continuously attached to the pressure transducer because of the possibility of thrombus formation. Thus, pulmonary arterial pressures were recorded only during chest pain. Lead II of the electrocardiogram was continuously monitored.

2. The patient's cardiac output was measured initially using either standard dye-dilution or thermodilution techniques. In addition, measurement was made of the arterial oxygen saturation and arteriovenous oxygen difference on admission and on at least a daily basis thereafter.

3. After 48 hours of hemodynamic monitoring, coronary arteriography was performed by the Judkins technique. This procedure was followed by left ventricular angiography performed with use of a no. 7F Cook pigtail catheter.

TABLE II

Hemodynamics During Unprovoked Anginal Episodes

	Prior to Pain	At Onset of Pain	After Nitroglycerin	*P* Value
Group I (5 episodes of pain)				
BA pressure (mm Hg)	120/63	122/69	120/70	
PA pressure (mm Hg)	18/9	17/10	19/10	
Heart rate (beats/min)	72 ± 1.4	85 ± 4.7	70 ± 2	<0.05
a-v O_2 difference (vol %)	4.6	...	...	
Cardiac output (liters/min)	5.6	...	...	
Group II (23 episodes of pain)				
BA pressure (mm Hg)	123/69	152/89	124/80	
PA pressure (mm Hg)	23/10	26/13	21/12	
Heart rate (beats/min)	79 ± 1.7	88 ± 2.8	84 ± 1.5	<0.01
a-v O_2 difference (vol %)	4.8	...	...	
Cardiac output (liters/min)	5.3	...	...	
Group III (28 episodes of pain)				
BA pressure (mm Hg)	126/70	166/95	119/70	
PA pressure (mm Hg)	21/12	36/20	19/14	
Heart rate (beats/min)	77 ± 1.7	78 ± 1.8	83 ± 2.2	NS
a-v O_2 difference (vol %)	4.7	...	...	
Cardiac output (liters/min)	5.2	...	...	

a-v O_2 = arteriovenous oxygen difference; BA = brachial arterial; NS = not significant; PA = pulmonary arterial.

4. A decision was made on the day of arteriography regarding the patient's subsequent management. If surgery was recommended, it was performed within 48 hours of the arteriography, or usually 72 hours after admission to the study.

Medical treatment during the period of hemodynamic monitoring was limited to sedation and administration of sublingual nitrates during anginal attacks. Propranolol, anticoagulant agents and long-acting nitrates were not given.

Results

Clinical Data

The clinical profile of the study patients is presented in Table I. The majority (24 of 26) were male patients with a background of stable exertional angina that, on exacerbation, prompted admission to the hospital. Typically, the change in ischemic chest pain was quite abrupt, occurring days to weeks before admission, and frequently it represented the onset of resting or nocturnal angina. Only two patients admitted to the study had experienced their first attack of anginal pain on the day of admission. Ten patients had prior myocardial infarction by standard criteria on the admission electrocardiogram; all 26 patients had ST-T wave abnormalities on admission suggestive of ischemia. Transient and reversible ST-T wave changes occurred during anginal episodes in most patients.

Hemodynamic Measurements

The 48 hour monitoring period provided data that allowed hemodynamic characterization of this patient population. During initial instrumentation, measurements were made of the brachial, pulmonary arterial and pulmonary arterial wedge pressures. Normal values were considered to be less than 12 mm Hg (mean) for the pulmonary arterial wedge, less than 35/10 mm Hg for the pulmonary artery and less than 140/90 mm Hg for the brachial artery. A cardiac index of 2.5 to 4.5 liters/min per m^2 was considered normal.

Initial hemodynamic data demonstrated normal values for the three pressure measurements and cardiac output in 25 of 26 patients during pain-free periods. The 26th patient, a 53 year old man, had an initial resting left ventricular end-diastolic pressure of 17 mm Hg. His daily serum enzyme determinations were consistent with the evolution of myocardial infarction but were not associated with electrocardiographic changes.

Hemodynamics during anginal episodes: Seventeen of the 26 study patients continued to have episodes of anginal pain at rest during the 48 hour monitoring period. Only those episodes of sufficient severity to require sublingual nitrates were included. The frequency of attacks ranged from 1 episode in each of five patients to a maximum of 13 episodes documented in one patient. There was an average of 2.6 anginal episodes per patient during the monitoring period.

The hemodynamic data obtained during the 56 episodes are summarized in Table II. Three types of hemodynamic abnormalities could be distinguished during pain. These changes represent observations made at the onset of pain. While the heart rate and brachial arterial pressure were continuously moni-

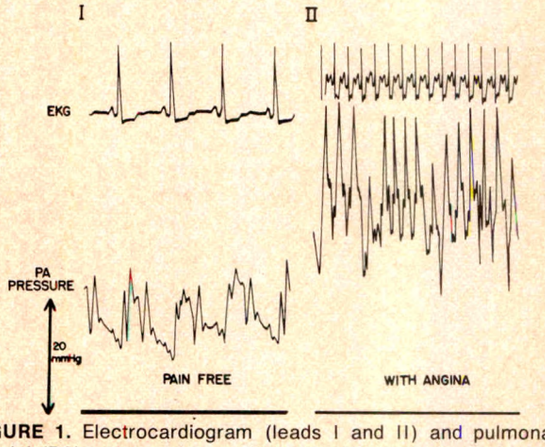

FIGURE 1. Electrocardiogram (leads I and II) and pulmonary arterial (PA) pressure in a patient in group III during a pain-free period and during angina. At the onset of pain, the pulmonary arterial pressure has increased from 23/10 to 53/23 mm Hg. Note the ischemic S-T segments during pain. Paper speed on the left is 25 mm/sec; that on the right is 10 mm/sec.

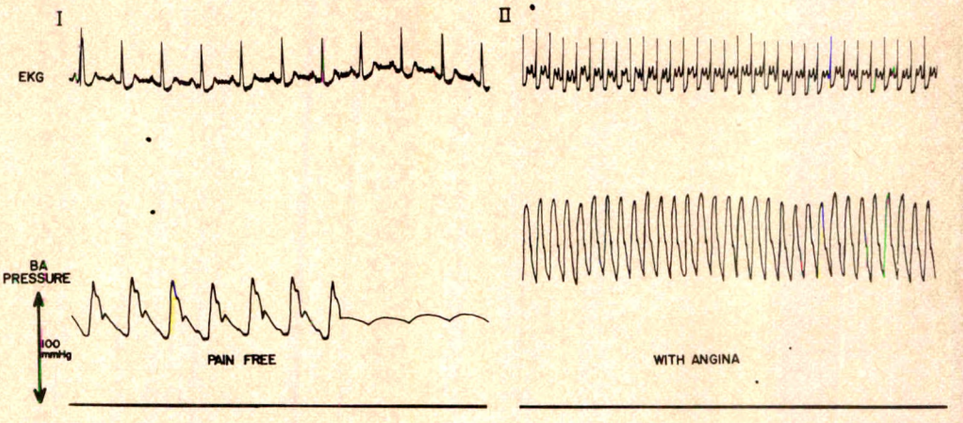

FIGURE 2. Brachial arterial (BA) pressure for the same patient during the same episode of pain. The pressure has increased from 110/50 mm Hg during an angina-free period to 200/110 during pain. Paper speeds as in Figure 1.

tored, notation was made of pressures at the onset of pain, typically less than 30 seconds after the start of pain. After the heart rate and brachial and pulmonary arterial pressures were determined, nitroglycerin was given and the response noted. Usually within 2 to 5 minutes the pain had subsided and the baseline condition was restored. In three patients (group I) there were no changes other than an increase in heart rate, averaging 15 beats/min. The brachial, pulmonary arterial and pulmonary arterial wedge pressures remained unchanged before and during pain. Another discrete subset of seven patients (group II) typically had an increase in brachial arterial pressure and heart rate before and during pain. A third group of seven patients (group III) had increased brachial, pulmonary arterial and pulmonary arterial wedge pressures before or during anginal attacks, or both. The latter group did not have an increase in heart rate with pain comparable to that observed in group I or II. The average increase in brachial arterial pressure for the latter two groups was 28 mm Hg systolic and 20 mm Hg diastolic. Patients who had increased pulmonary arterial pressure during pain had an average increase of 15 mm Hg systolic and 8 mm Hg diastolic. No patient had clinical evidence of pulmonary vascular congestion with these increases in pulmonary arterial pressure. In no case did an increase in pulmonary arterial or pulmonary arterial wedge pressure precede an increase in brachial arterial pressure or heart rate. Examples of pressure changes noted in one patient during pain are shown in Figures 1 and 2. In all patients who had more than one period of chest pain, the hemodynamic responses during later episodes of pain were similar to those of the first episode.

In five patients a significant increase in brachial arterial pressure preceded the subjective awareness of anginal pain by 5 to 10 minutes (Fig. 3). Four of these five patients were in the group in which both brachial and pulmonary arterial pressures increased with pain.

Coronary Arteriography

The coronary arteriographic and left ventriculographic findings in the 25 patients studied are shown in Table III. Eighty percent of the patients (20 of 25) had double or triple vessel occlusive coronary disease with greater than 70 percent narrowing. More than 50 percent (14 of 25) had associated contractile abnormalities on review of the left ventriculogram. All these studies were completed without complication.

Clinical Course

The subsequent clinical course for the study group is outlined in Table IV. Three of the patients experienced myocardial infarction during the observation period, as diagnosed by a rise in serum glutamic oxaloacetic transaminase (SGOT) levels to more than 50 percent above normal. There was no characteristic hemodynamic pattern before infarction in these three patients, except in the previously mentioned patient with increased left ventricular end-diastolic pressure at rest. None of the infarctions were transmural as defined by the development of Q wave patterns on the electrocardiogram, and all were diagnosed by enzyme changes alone. All patients survived. Four patients were not operated upon for nonmedical reasons, typically because of reluctance by the patient or his referring physician to consider surgery. The remaining 19 patients had cardiac operations on either day 3 or 4 of their hospitalization. Seven patients had a single saphenous vein bypass graft; 12 had a double graft. In addition, two patients had associated right coronary gas endarterectomy. All survived operation and were discharged from the hospital. During operation, two patients had new Q waves diagnostic of myocardial infarction; both of these patients did well clinically postoperatively.

Discussion

Although an extensive literature has recently emerged concerning the indications and results of aortocoronary artery saphenous vein bypass surgery for the patient with unstable angina, few studies have reported the hemodynamic status of these patients during both pain and pain-free periods.[7-13] An important feature in understanding the success or failure of this surgical procedure is the analysis of the hemodynamic status of the patient with unstable angina in three conditions: during pain-free periods, during episodes of unprovoked angina pectoris, and

TABLE III

Angiographic Findings in 25 Patients

	no.
Coronary arteriogram (>70% occlusion)	
Single vessel	10
Two vessels	10
Three vessels	5
Left ventricular angiogram	
Mitral regurgitation	3
Hypokinesis, akinesis	14

TABLE IV

Clinical Outcome in 26 Patients

	no.
Acute myocardial infarction	3
Medical treatment	4 without infarction
Surgical treatment	
Single bypass	7
Double bypass	12
Gas endarterectomy (right coronary)	2

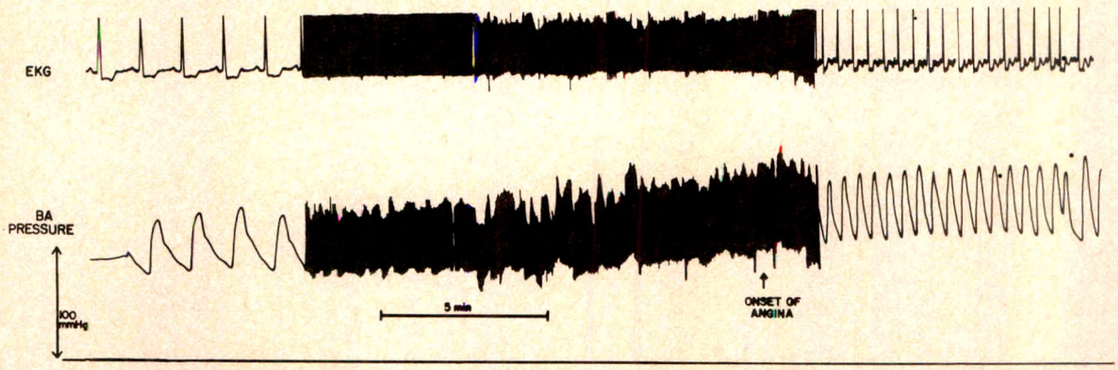

FIGURE 3. A continuous recording of brachial arterial (BA) pressure before and during angina. To the far left the brachial arterial pressure is 120/80 mm Hg at a paper speed of 25 mm/sec. The paper speed has been reduced to 0.25 mm/sec in the center section of the illustration. Note that the brachial arterial pressure began to increase 15 minutes before the patient was aware of chest pain. With the onset of angina the brachial arterial pressure increased to 180/110 mm Hg. Paper speed at the far right is 10 mm/sec.

after operation. This report summarizes our experience with 26 consecutive, carefully selected patients having unstable angina and confirmed severe occlusive coronary artery disease. Significant coronary artery disease (greater than 70 percent narrowing of at least one vessel on coronary arteriograms) was mandatory for inclusion in this study. Such arteriographic documentation is important, since four additional patients (not included in our series) initially underwent monitoring because their clinical presentation and electrocardiograms suggested unstable angina, but arteriograms showed either normal or only minimally diseased coronary arteries. The questionable statistical validity of studies reporting the clinical course of large series of similar patients without arteriographic confirmation of coronary disease makes comparison among patient series difficult.[14]

The normal resting, pain-free hemodynamic measurements contrast sharply with those of patients having established acute myocardial infarction; many of the latter patients demonstrate gross hemodynamic alterations, including abnormalities in arteriovenous oxygen difference, cardiac index and left ventricular end-diastolic pressure.[15,16] The extent of these abnormalities relates to the severity of left ventricular failure, or changes in compliance secondary to the acute infarction. In patients with acute myocardial infarction but without clinical heart failure, Ramo et al.[15] observed abnormalities including widened arteriovenous oxygen differences in 45 percent of patients, and reduced cardiac index (less than 3 liters/min per m^2) in 51 percent. The only abnormality noted among our patient population was increased left ventricular end-diastolic pressure (17 mm Hg) in one patient who was later demonstrated to have had a subendocardial infarction.

Robinson[17] has discussed in detail the relation of heart rate and systolic blood pressure to the onset of anginal pain. All 17 patients having spontaneous angina had changes in one or both of these variables, leading to an increase in cardiac work and increased myocardial oxygen demand. These changes apparently accompanied or, in some cases, preceded the pain, although a component of this hemodynamic response may well be a response to the pain itself. Five patients had a well documented increase in brachial arterial pressure 5 to 15 minutes before the onset of subjectively recognized chest pain. Four of these patients were classified in group III and one in group II. This small number suggests that angina at rest is precipitated by an autonomically mediated sympathetic discharge, with consequent increases in systemic vascular resistance and heart rate, resulting in increased cardiac work.[18] Administration of nitroglycerin was uniformly effective in relieving the chest pain; however, the decrease in systolic blood pressure usually occurred before the patient experienced relief of the angina. Blood catecholamine levels were not measured during anginal attacks.

Any given patient showed the same accompanying hemodynamic abnormalities during each episode of pain, and systolic blood pressure and heart rate product were closely correlated during each episode. These results are comparable to the observations of Scheidt et al.[19] and Roughgarden,[20] who found hemodynamic changes consisting of increased brachial arterial pressure or abnormal left ventricular function preceding subjective angina in a small number of patients. We were unable to correlate the type of associated hemodynamic changes with the location or severity of occlusive coronary artery disease, absence or presence of abnormalities of contraction by left ventricular angiography, or number of previous myocardial infarctions.

Hemodynamic basis for angina pectoris: The hemodynamic monitoring methods used in our study do not allow definitive comment on the sequence of physiologic events antedating the onset of pain in these patients with angina at rest. Continuous monitoring of left ventricular and pulmonary arterial pressures with serial determination of cardiac index during pain will be necessary if the true sequence of

causal factors is to be determined. Our data support Gorlin's thesis that angina at rest may be caused by an episode of acute peripheral vasoconstriction, perhaps related to release of catecholamines.[18] This thesis would explain the increased heart rate in the patients in group I. The patients in group III whose pulmonary arterial and pulmonary arterial wedge pressures increased with angina are of importance, since the altered pulmonary arterial diastolic pressures suggest that left ventricular dysfunction is a feature, if not the primary cause, of the anginal attack. Altered left ventricular compliance as a response to the ventricular hypoxia would be one explanation for this observation.[6] Alternatively, the development of reversible acute heart failure due to alterations in both left ventricular pressure and volume could also explain the results obtained in patients in group III. Scheidt et al.[19] described three patients who had six episodes of pain preceded by an increase in left ventricular end-diastolic pressure without associated changes in arterial pressure or heart rate, but the mechanism of this change is unclear. Only a critical sequential analysis of the hemodynamic events will allow more careful cause and effect analysis of the unprovoked anginal attack in the patient with unstable angina. Such studies are currently underway.

Prognostic significance of hemodynamic findings: The subsequent clinical course of the 26 patients could not be predicted from the presence or absence of continued angina at rest or the type of hemodynamic abnormalities associated with resting angina. Three patients had myocardial infarction as demonstrated by serum enzyme changes. None of these patients had subsequent pain in the hospital, possibly because of infarction of the ischemic area. Nineteen patients had coronary bypass surgery without any hospital mortality. These 19 were equally distributed among those patients having no pain at rest in the hospital in groups I, II and III. We thus conclude that the resting and pain-associated hemodynamic status was not helpful in distinguishing the high risk patient for early myocardial infarction or operative death in this small group.

The abnormal hemodynamic status, particularly changes in left ventricular compliance, may well be an important cause of the unstable nature of the angina or a precipitating factor in myocardial infarction. The high percentage of patients who had early coronary bypass surgery did not permit further analysis of this point. Continuing accumulation of hemodynamic data on patients with unstable angina should provide more comprehensive information regarding this problem.

Acknowledgment

We gratefully acknowledge the technical assistance of Miss Jan Gross in the performance of these studies.

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Maximal Cardiac Output During Exercise in Patients with Coronary Artery Disease

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Cardiac output, determined by the direct Fick method, was measured each minute during multistage treadmill testing in which patients exercised to the point of exhaustion. Twenty-nine tests and 183 measurements of cardiac output during exercise were performed in 16 patients with coronary artery disease. Maximal cardiac output paralleled the maximal oxygen intake and was reflected by a plateau during the final minutes of exercise. Significant decreases in stroke volume and increases in mean pulmonary arterial pressure suggest that acute left ventricular dysfunction is the mechanism limiting the maximal cardiac output in these patients. Maximal cardiac output is a sensitive and fundamental indicator of the degree of impairment resulting from coronary disease, and has potential value in defining the role of various methods of treating this disease.

This report describes the results of assessment of cardiac output during exercise in patients with coronary artery disease who underwent treadmill stress testing to the point of exhaustion.

Methods

Patients: Fifteen men and one woman with coronary artery disease, observed in an academic cardiology service, were selected for study. Three had prior transmural myocardial infarction diagnosed by typical pain syndrome, enzyme changes and evolving electrocardiograms that were diagnostic during the patients' admission to the coronary care unit and while they were under our supervision. The remaining 13 patients had angina pectoris and had undergone selective coronary arteriography and left ventricular angiography. Since several patients had repeat hemodynamic tests on different days, this report provides an analysis of 29 studies. Anthropometric, clinical and angiographic data on the 16 patients are shown in Table I.

Ergometry: Studies were performed with patients in the basal fasting state after completion of a physical examination and 12 lead electrocardiogram and after giving informed consent. Initial tests were carried out using the multistage continuous treadmill methods of Bruce et al.[1,2] and Doan et al.[3] Monitoring of pressures, heart rate and electrocardiogram during exercise and the first few minutes of recovery was performed by one or more physicians; a defibrillator, ventilator, oxygen and drugs[4] for emergency use were always available. The second (hemodynamic) test was performed days to weeks later and consisted of the multistage treadmill test of Bruce et al., with the addition of a less strenuous 3 minute initial stage with the patient walking at 1.7 miles/hour at zero elevation. Each 3 minute work load was followed by a step increase to the next stage without intervening rest, and the patient was asked to continue until exhausted. After exercise the patient was monitored in the supine position until the electrocardiogram, pressures and heart rate returned to preexercise levels.

Catheterization: A balloon flow-directed soft polyvinyl catheter (Swan-Ganz no. 7F) was advanced to the pulmonary artery by way of a cutdown procedure on the median basilic vein during monitoring of pressure. Ectopic beats seldom occurred and were never a problem. The catheters were

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TABLE I

Anthropometric, Clinical and Angiographic Data

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Age (yr)	55	64	52	40	50	61	50	63	54	54	63	61	48	52	60	61
Wt	75.8	78.0	81.6	92.5	70.3	90.7	54.9	81.9	95.2	63.0	93.4	75.1	85.3	72.6	66.7	76.6
BSA	1.85	2.00	1.98	2.06	1.83	2.12	1.54	2.01	2.19	1.69	2.19	1.81	1.96	1.82	1.78	1.96
BP	140/70	158/80	138/70	130/82	160/92	130/80	160/90	150/80	145/82	126/80	140/85	136/90	130/84	130/80	130/80	140/86
AP	Atypical	0	+	0	Atypical	+	+	+	+	+	+	+	+	+	+	+
Cor Insuf	0	0	0	0	7/71	2/72	—	—	—	—	—	9/72	10/71	—	—	3/70
MI	AMI 6/71	IMI 7/71	0	IMI 12/70	0	0	—	—	—	AMI 11/70	—	—	—	IMI 2/72	IMI 62	—
ECG, rest	AMI	IMI	LVI	NI	NI	NI	NI	IMI	LVI	AMI	NI	NI	NI	IMI	IMI	NI
ECG, ex	NI	NI	ST ↓ 2 mm	NI	NI	ST ↓ 4 mm	NI	ST ↓ 5 mm	ST ↓ 3 mm	NI	ST ↓ 2 mm	ST ↓ 3 mm	ST ↓ 1 mm	ST ↓ 3 mm	ST ↓ 3 mm	ST ↓ 1 mm
LVSP	130	...	150	...	160	115	125	155	100	...	108	120	120	130	100	138
LVEDP	8	...	14	...	6	7	7	25	8	...	12	15	12	15	9	10
LV vol	NI	...	NI	...	NI	NI	NI	SI ↑	NI	...	NI	NI	NI	NI	NI	NI
LVEF	NI	...	NI	...	NI	NI	NI	SI ↓	NI	...	NI	NI	NI	NI	NI	NI
LV con	NI	...	NI	...	NI	NI	NI	Inf Ak	NI	...	NI	NI	NI	NI	NI	NI
LCA	NI	...	NI	...	NI	NI	NI	40%	NI	...	NI	NI	NI	NI	NI	NI
LCF	NI	...	NI	...	NI	NI	NI	100%	100%	...	50%	100%	NI	NI	NI	NI
LAD	90%	...	100%	...	80%	75%	NI	50%	90%	...	100%	100%	100%	100%	70%	90%
RCA	NI	...	50%	...	NI	100%	100%	100%	100%	...	100%	90%	NI	100%	90%	NI
NYHA FC	III	II	II	II	II	III	III	III	III	II	III	III	III	II	III	III
FAI	55	20	45	20	50	60	45	43	45	15	58	70	45	26	25	50

AMI = anterior myocardial infarction; AP = angina pectoris; BP = cuff blood pressure (mm Hg); BSA = body surface area (m^2); Cor insuf = coronary insufficiency; ECG, ex and rest = exercise and resting electrocardiograms, respectively; FAI = functional aerobic impairment (Bruce et al.[1]); IMI = inferior myocardial infarction; Inf Ak = inferior akinesia; LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCF = left circumflex coronary artery; LV con = cineangiographic segmental left ventricular contraction pattern; LVI = left ventricular ischemia; LV vol = cineangiographic left ventricular end-systolic and end-diastolic volumes; LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEF = cineangiographic left ventricular ejection fraction; LVSP = left ventricular systolic pressure (mm Hg); MI = history of myocardial infarction; NI = normal; NYHA FC = New York Heart Association functional class; RCA = right coronary artery; SI ↓ = and SI ↑ = slight decrease and increase, respectively; ST ↓ = S–T segment depression; Wt = weight (kg).

+ = present; — = absent; ... = not studied; % = percent narrowing of vessel diameter on arteriogram.

easily and rapidly (15 to 60 seconds) advanced to the pulmonary artery without fluoroscopy as described by Swan et al.[5]

A systemic artery, either the radial or brachial, was entered percutaneously using direct needle puncture with a short catheter advanced over the needle or over a guide wire using the Seldinger technique (Bardic 18.5 g, Jelco 16 g or Longdwell 16 g) and fixed to the skin by suture.

Pressure measurements: Transducers (Kulite P5L-125-6) were applied directly to the ends of the catheters and connected to carrier amplifiers (Brush Instrument RD 4212); pressure was obtained on a Brush Instruments Mark 240 recorder.

After balancing, the transducers were calibrated against a mercury column immediately before each test. The transducers were leveled at the mid-axillary line with the patient in the supine position and at the fourth interspace anterior axillary line with the patient upright. During standing and exercise, the catheterized arm was supported by an adjustable cradle fastened to the support bars of the treadmill to maintain the relation of transducers to the fourth interspace during changes in grade of the walking platform. Phasic and mean systemic and pulmonary arterial pressures were measured under the following conditions: supine and standing rest, exercise and supine recovery. Pulmonary wedge pressures were measured during supine rest and again during supine recovery. Wedge pressure determinations were not attempted during exercise. Sensitivity was 5 mm Hg/mm for systemic arterial pressure recording and 1 mm Hg/mm for pulmonary arterial pressure recording. Recording speeds were 5 and 25 mm/sec.

Oxygen intake: Exhaled air was collected in 120 liter neoprene bags at 1 minute intervals, with volume measured by spirometer and oxygen and carbon dioxide content by the Scholander technique, using standard formulas for calculation of oxygen intake ($\dot{V}O_2$). Paramagnetic (Beckman E-2) analysis of gas samples was also carried out after water vapor was removed and before and after removal of carbon dioxide; as expected, results of the two methods were in close agreement. The standard error of the difference (SEd)* of 17 samples calculated by both methods in $\dot{V}O_2$ liters per minute was 0.022.

Blood oxygen content: Blood, drawn anaerobically into heparinized syringes, was analyzed on the same day with use of the van Slyke manometric method. Samples from the pulmonary and systemic arteries were obtained simultaneously and timed to the mid-period of exhaled air collection. The relatively large lumen of the Swan-Ganz no. 7F catheter enabled removal of 5 to 7 ml samples in 9 to 12 seconds. Precision of measurement by van Slyke was assessed in duplicate aliquots from 41 consecutive samples, and by single measurements of 32 pairs of samples drawn in two syringes in immediate sequence from either arterial or mixed venous blood. Standard error of the difference of oxygen content in milliliters per liter for aliquots was 0.95, and for consecutive samples 2.25. During the exercise studies, single rather than paired samples were drawn simultaneously from pulmonary and systemic arteries to allow for more frequent sampling.

Cardiac output: Cardiac output was calculated by the direct Fick method on the basis of the measurements described, with use of standard formulas. Heart rate was measured from the continuously recorded electrocardiogram. Stroke volume was calculated in standard manner as the ratio of cardiac output and heart rate.

*SEd = $\sqrt{\frac{\Sigma d^2}{2k}}$, where d = difference between replicates of k pairs.[6]

TABLE II

Indexes of Oxygen Transport (means and standard deviations)

	$\dot{V}O_2$	SaO_2	PaO_2	a-v O_2	$\dot{Q}$	HR	SV
Supine rest	0.255	167	123	44	5.84	69	87
	±0.05	±15	±14	±7	±1.29	±12	±27
Exercise							
Minus 4	1.299	177	63	113	11.29	125	92
minutes	±0.36	±15	±13	±17	±2.78	±18	±25
Minus 3	1.440	178	60	118	12.29	131	96
minutes	±0.44	±14	±14	±17	±3.27	±18	±27
Minus 2	1.572	180	56	124	12.92	140	94
minutes	±0.48	±13	±15	±20	±3.55	±17	±26
Minus 1	1.768	181	52	129	13.57	148	93
minute	±0.53	±16	±12	±20	±3.60	±17	±26
Final minute	1.782	181	47	134	13.38	154	89
	±0.54	±13	±11	±18	±3.65	±17	±25

a–v O_2 = arteriovenous oxygen difference (ml/liter); HR = heart rate (beats/min); PaO_2 = pulmonary arterial oxygen content (ml/liter); $\dot{Q}$ = cardiac output (liters/min); SaO_2 = systemic arterial oxygen content (ml/liter); SV = stroke volume (ml); $\dot{V}O_2$ = oxygen intake (liters/min).

Results

Cardiac output and oxygen intake: The data consist of 183 measurements of cardiac output dur-

TABLE III

Hemodynamic Responses to Exercise (Paired *t* Tests of Significance of Differences)

	$\dot{V}O_2$		$\dot{Q}$		a–v O_2		SV		HR	
	t	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
FM vs −1	0.78	NS	1.06	NS	2.41	<0.02	2.99	<0.005	7.61	<0.001
−1 vs −2	8.22	<0.001	2.41	<0.02	4.02	<0.001	0.19	NS	10.4	<0.001
−2 vs −3	8.21	<0.001	3.39	<0.001	4.01	<0.001	0.78	NS	10.2	<0.001
−3 vs −4	4.88	<0.001	2.41	<0.02	2.81	<0.005	0.53	NS	10.1	<0.001

FM = final minute of exercise; NS = not significant. −1 to −4 = minus 1 to minus 4 minutes of exercise. Other abbreviations as in Table II.

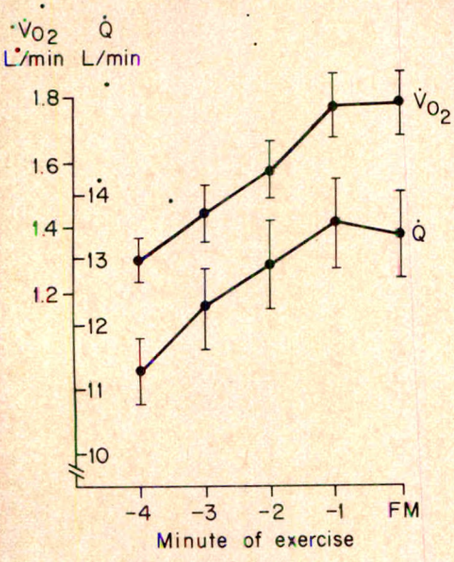

FIGURE 1 (left). Oxygen intake ($\dot{V}O_2$) and cardiac output ($\dot{Q}$) during exercise in patients with coronary artery disease. Plateau levels indicate maximal values. Mean values (liters/min) ±1 standard error are presented. FM = final minute of exercise.

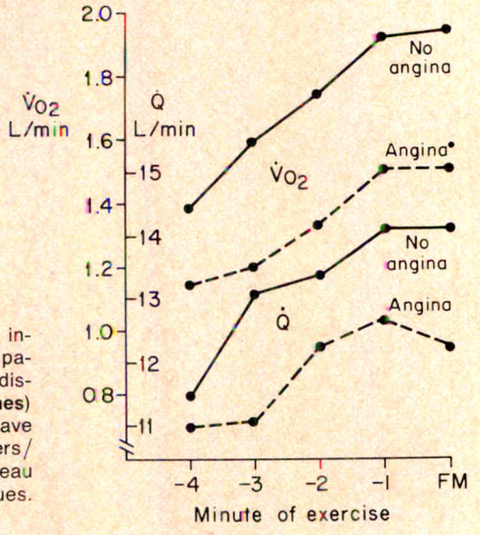

FIGURE 2 (right). Oxygen intake and cardiac output in patients with coronary artery disease who did (**broken lines**) and did not (**solid lines**) have angina. Mean values (liters/min) are presented. Plateau levels indicate maximal values. Abbreviations as in Figure 1.

ing exercise. Table II contains mean values for the various indexes of oxygen transport during the final minute of symptom-limited exercise and the preceding 4 minutes. The cardiac output and oxygen intake data are shown in Figure 1. Both indexes increased significantly during exercise until the final minute of exercise when both leveled off without further significant change (Table III). The data were analyzed further, comparing the results in patients with angina and those with healed myocardial infarction, patients given nitroglycerin sublingually immediately before exercise and those not so treated, and patients who experienced anginal pain during exercise and those who did not. All groups showed an increase of cardiac output and oxygen intake with increasing exercise and a leveling off of both variables during the final minute (Table IV). In one analysis (Fig. 2), the results of the 29 tests were divided into those of 11 patients who had anginal pain during exercise and 18 patients who did not. The results in both groups plateaued at the final minute of exercise, but the lower values in the group with chest pain reflected the greater impairment of oxygen transport in these patients.

Arteriovenous oxygen difference: Blood oxygen content data (Tables II and III, Fig. 3) demonstrated the marked changes in blood oxygen levels between the conditions of supine rest and maximal exercise. A slight but significant increase in systemic arterial oxygen content was associated with a marked reduction in pulmonary arterial oxygen, which reached a nadir of 47 ml/liter during the final minute of exercise. Progressive widening of the arteriovenous oxygen difference occurred with exercise up to a mean level of 134 ml/liter in the final minute.

Arterial pressures: During exercise, systemic pressure showed a marked increase during systole but only slight changes during diastole. Pulmonary arterial mean pressure also increased slightly during exercise. Pulmonary wedge pressures decreased significantly between the conditions of supine rest before exercise and the early supine recovery period (30 to 90 seconds after termination of exercise) (Table V).

TABLE IV

Mean Oxygen Intake and Cardiac Output in Patients with Coronary Artery Disease Classified According to Presence of Angina During Exercise, Prior Myocardial Infarction or Use of Nitroglycerin Before Exercise

	Oxygen Intake (liters/min)						Cardiac Output (liters/min)					
Minute of Exercise	AP (11)	No AP (18)	MI (8)	No MI (21)	NG (14)	No NG (15)	AP (11)	No AP (18)	MI (8)	No MI (21)	NG (14)	No NG (15)
Minus 4	1.148	1.383	1.584	1.184	1.228	1.361	10.99	11.46	13.06	10.67	10.79	11.75
Minus 3	1.194	1.594	1.806	1.306	1.361	1.519	11.02	13.09	14.21	11.59	11.55	13.03
Minus 2	1.332	1.737	2.006	1.420	1.479	1.672	12.26	13.37	14.61	12.32	12.50	13.37
Minus 1	1.502	1.916	2.228	1.584	1.637	1.899	12.71	14.08	15.24	12.87	13.08	14.03
FM	1.507	1.950	2.182	1.630	1.677	1.880	12.23	14.08	14.69	12.88	12.73	13.99

Figures in parentheses indicate number of subjects. AP = angina pectoris during exercise; FM = final minute of exercise; MI = healed myocardial infarction; NG = nitroglycerin, 0.4 mg sublingually before exercise.

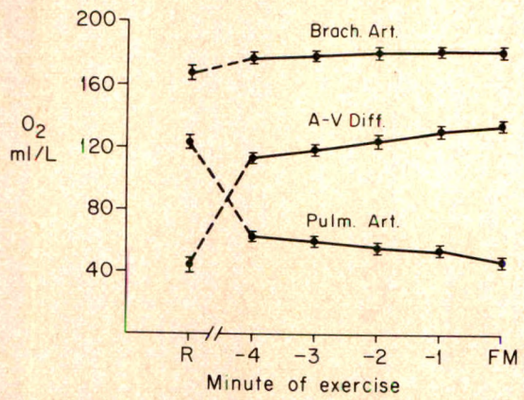

FIGURE 3. Blood oxygen content during exercise in patients with coronary artery disease. Mean values (ml/liter) ±1 standard error are presented. A-V Diff. = arteriovenous oxygen difference; Brach. Art. = brachial artery; FM = final minute of exercise; Pulm. Art. = pulmonary artery; R = rest.

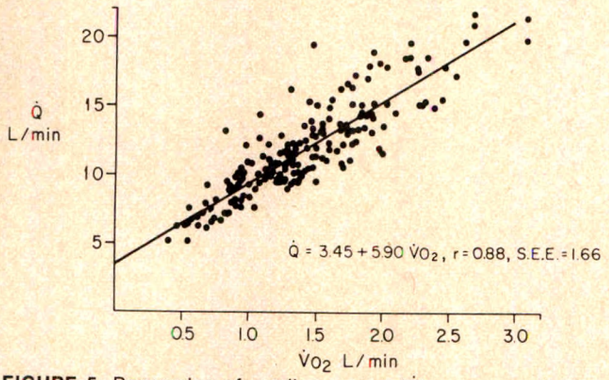

FIGURE 5. Regression of cardiac output ($\dot{Q}$) on oxygen intake ($\dot{V}O_2$) in 183 measurements obtained during exercise in patients with coronary artery disease. r = coefficient of correlation; S.E.E. = standard error of the estimate.

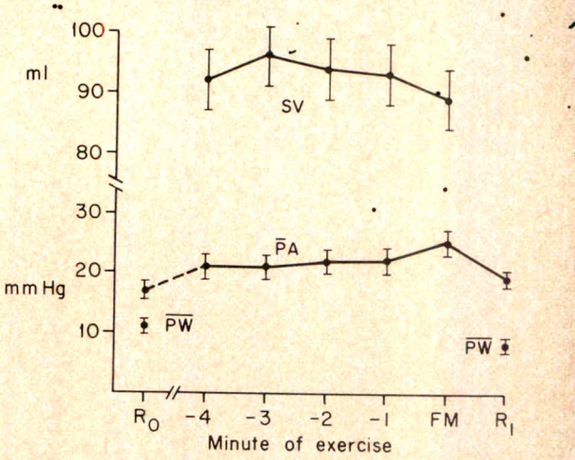

FIGURE 4. Stroke volume (SV) and mean pulmonary arterial pressure ($\bar{P}A$) during exercise in patients with coronary artery disease. Mean values ±1 standard error are presented. FM = final minute of exercise; $\overline{PW}$ = pulmonary wedge pressure; R_0 = rest; R_1 = early recovery.

Stroke volume: Stroke volume increased slightly but significantly between the conditions of supine rest and upright exercise. The differences in stroke volume were not significant with increasing exercise until the final minute, when a highly significant decrease in stroke volume occurred (Table III). The increase in mean pulmonary arterial pressure between the minute preceding the final minute of exercise (22 mm Hg) and the final minute (25 mm Hg) was also significant (t = 2.11, P <0.05). The sequential data on stroke volume and mean pulmonary arterial pressure are shown in Figure 4.

Regression and prediction: A regression analysis of cardiac output on oxygen intake was carried out for the 183 measurements made during exercise

TABLE V

Brachial and Pulmonary Arterial Pressures (means and standard deviations)

	Brachial Arterial Pressure (mm Hg)			Pulmonary Arterial Pressure (mm Hg)		
	Systolic	Diastolic	Mean	Mean	Wedge	HR × SBP
Supine rest	155	83	112	17	11	107
	27	12	17	5.3	4.9	22
Exercise						
Minus 4 minutes	176	83	...	21	...	227
	27	11	...	5.5	...	44
Minus 3 minutes	180	84	...	21	...	235
	24	11	...	6.8	...	37
Minus 2 minutes	188	84	...	22	...	264
	26	11	...	7.1	...	45
Minus 1 minute	187	86	...	22	...	279
	30	12	...	7.5	...	52
Final minute	192	88	...	25	...	296
	32	13	...	6.5	...	58
Early recovery, supine	175	87	119	19	8	186
	28	28	21	5.1	4.5	41

HR × SBP = product of heart rate and brachial arterial systolic pressure divided by 100.

(Fig. 5). The regression equation found for these patients with coronary artery disease was $\dot{Q} = 3.45 + 5.90\ \dot{V}O_2$ ($r = 0.88$, standard error of the estimate [SEE] = 1.66).

Predictors of maximal cardiac output are listed in Table VI. The maximal heart rate and double product of heart rate and maximal systolic pressure proved disappointing predictors. Test duration, although better, was not a good predictor. Maximal oxygen intake showed the highest correlation, but the high standard error precludes its use as a good predictor. Maximal stroke volume (SV_{max}), although somewhat better ($\dot{Q}_{max} = 1.91 + 0.13\ SV_{max}$ [$r = 0.87$, SEE = 1.83]), offers no advantage since it requires the measurement of cardiac output for its derivation.

TABLE VI

Predictors of Maximal Cardiac Output in Patients with Coronary Artery Disease

Predictor	Correlation Coefficient (r)
Maximal oxygen intake ($\dot{V}O_2$)	0.89*
Test duration	0.57
Maximal heart rate (HR max)	0.26
Product of HR max and maximal brachial arterial systolic pressure	0.22

* Maximal cardiac output = 2.52 + 6.09 $\dot{V}O_2$ max, standard error of the estimate = 3.68.

Discussion

In 1955, Taylor et al.[7] demonstrated the maximal oxygen consumption of normal subjects as a fundamental measure of circulatory performance. They combined increasingly strenuous treadmill exercise with serial measurements of oxygen intake and observed that the obligatory increase in oxygen consumption with increasing treadmill work reached a plateau that defined the capacity of the oxygen transport system and usually corresponded to subjective feelings of extreme exhaustion.

Similar patterns reflecting the maximal oxygen intake and maximal cardiac output were found for our patients with coronary artery disease. Maximal cardiac output occurred both in patients with angina and in those with healed infarction, and in patients who experienced anginal pain during exercise as well as those who did not.

The decreasing stroke volume and increasing pulmonary arterial pressure that occurred during the final minute of exercise would appear to reflect acute left ventricular impairment or failure, which is rapidly reversed during the initial seconds of recovery after exercise. Acute reduction in left ventricular performance thus seems to be the mechanism responsible for limiting the maximal cardiac output in these patients.

Comparison of normal men and those with coronary disease: Analysis of the regression of cardiac output on oxygen consumption is of interest when compared to findings in normal men of similar age. Granath et al.[8] using submaximal bicycle exercise found a value of $\dot{Q} = 3.01 + 6.00\ \dot{V}O_2$; whereas Grimby et al.[9] found the relation in nine endurance athletes to be $\dot{Q} = 8.3 + 5.2\ \dot{V}O_2$ and noted the higher intercept in physically trained than in untrained persons. The regression equation for men with coronary artery disease (Fig. 5) is nearly identical to that seen for normal men. One might have anticipated a smaller slope for the patients with coronary disease, reflecting more oxygen extraction to compensate for less cardiac output, and thus to conserve the work of the heart, but this was not so. It is there-

TABLE VII

Comparative Mean Circulatory Data at Maximal Exercise

Subjects (no.) and Study	Age (yr) Range	Age (yr) Mean	Hgb	Wt	Syst. Art. Press. (SDM)	$\dot{V}O_2$	a–v O_2	$\dot{Q}$	HR	SV
Young trained men (6) (Åstrand, cited in Grimby et al.[9])	20–30	25	14.6	77	NA	4.93	171	28.9*	185	161
Young untrained men (8) (Saltin, cited in Grimby et al.[9])	19–27	23	14.0	70	NA	3.10	136	22.8*	198	116
Older trained men (9) (Grimby et al.[9])	45–55	51	13.5	70	203/92/134	3.56	133	26.8*	171	163
Older untrained men (15) (Hanson et al.[10])†	40–49	45	NA	74	172/79/111	2.74	133	20.6*	168	122
Older men with CAD (27) (present study)	40–63	55	14.4	80	192/88/...	1.86	136	13.8‡	155	92

* Dye-dilution method.
† Values near maximal.
‡ Direct Fick method.
a–v O_2 = arteriovenous oxygen difference (ml/liter); Hgb = hemoglobin (g/100 ml); HR = heart rate (beats/min); NA = not available; $\dot{Q}$ = cardiac output (liters/min); SV = stroke volume (ml); Syst. Art. Press. (SDM) = systemic arterial pressure, systolic, diastolic, mean (mm Hg); $\dot{V}O_2$ = oxygen intake (liters/min); Wt = weight (kg).

fore reasonable to infer from these data that acute left ventricular dysfunction, which occurs in the final minute of exercise and limits the maximal cardiac output, is preceeded by a normal response of the cardiac output at all submaximal levels of exercise.

A further comparison of maximal oxygen transport variables is seen in Table VII.[9,10] Hemodynamic variables in normal men in two contrasting age groups selected to compare trained athletes with untrained average men are compared with data in men with coronary artery disease. Several of the contrasts are of interest. Male athletes, young or old, typically have a high level of stroke volume and cardiac output; in younger but not older athletes, the maximal arteriovenous oxygen difference can be widened in excess of 170 ml/liter, thus allowing a proportionately greater maximal oxygen consumption in younger athletes. Physically trained men also show less deterioration of the maximal oxygen intake with advancing age than untrained men.[11]

A 33 percent reduction of maximal cardiac output of men with coronary disease compared to findings in older untrained men is accounted for by a 25 percent reduction in maximal stroke volume and an 8 percent reduction in maximal heart rate. The maximal arteriovenous oxygen differences are similar.

Other hemodynamic studies of exercise in cardiac patients include several in subjects without coronary artery disease[12-15] and others using submaximal tests in patients with coronary disease.[16-19] Detry and Bruce[20] demonstrated the effect of nitroglycerin on increasing maximal oxygen intake, and Detry et al.[21] demonstrated significant improvement in maximal oxygen intake after exercise training in patients with coronary artery disease. Murray et al[22] performed graded treadmill exercise studies in five patients with severe angina, and noted abnormalities in oxygen transport, depressed cardiac output and stroke volume, and widened arteriovenous oxygen difference before the onset of angina. Blackmon et al.[23] studied hemodynamic responses to maximal exercise in patients with tight mitral stenosis.

Our study appears to be the first to present data on maximal cardiac output in patients with coronary artery disease. This is rather surprising since this variable is a sensitive and fundamental indicator of the degree of impairment resulting from coronary disease. The studies appear to be safe since no serious complications or sequellae (such as ventricular fibrillation or myocardial infarction) occurred during these 29 tests in patients with coronary artery disease or in 14 additional tests in other patients with cardiac disease and a few normal subjects.

Acknowledgment

We acknowledge the assistance of S. Underhill, J. Bradley, E. Foley, L. Foard, E. Lapin, MD, H. Alvarez, MD, and C. Hansing, MD. The support and helpful comments of R. A. Bruce, MD are especially appreciated.

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Effects of Submaximal Isometric Handgrip on Left Ventricular Size and Wall Motion

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To evaluate the effects of sustained submaximal isometric handgrip exercise on the left ventricle in patients with previous myocardial infarction, we utilized the noninvasive techniques of radarkymographic video tracking, measurement of the left heart dimension and calculation of systolic time intervals to assess alterations in wall motion and left ventricular size and function during handgrip exercise performed at a tension level of 15 percent of maximal voluntary contraction. In 9 of 12 patients with dyskinesis or asynchrony at rest the mean amplitude and velocity of systolic outward movement increased during handgrip exercise ($P < 0.05$), whereas in 11 patients with initially hypokinetic areas mean amplitude and velocity decreased ($P < 0.05$); in 3 patients dyskinesis was produced de novo. In all 12 patients both amplitude and velocity decreased in areas of normal wall motion ($P < 0.05$); similar changes occurred in 5 normal control subjects. Alterations in systolic time intervals during handgrip exercise were variable, and no consistent patterns were observed in either patients or control subjects. In seven patients whose left heart dimension increased during handgrip exercise, wall motion abnormalities were more severe at rest than in the five patients whose left heart dimension decreased. The five control subjects showed a decrease in left heart dimension during handgrip exercise.

We conclude that the normal response to submaximal isometric handgrip exercise at 15 percent of maximal voluntary capacity is a decrease in left ventricular size and a reduction in both the amplitude and velocity of left ventricular wall motion. Furthermore, in patients with previous myocardial infarction sustained isometric handgrip exercise is a useful maneuver for the intensification or induction of left ventricular wall motion abnormalities. By contrast, no consistent alterations in systolic time intervals were observed during handgrip exercise either in normal subjects or in patients with previous myocardial infarction. Thus, systolic time intervals do not appear to be useful for evaluating the left ventricular response to submaximal handgrip exercise in individual patients.

Little information is available on alterations in left ventricular size and wall motion induced by submaximal handgrip exercise, although it would be desirable to have reliable, noninvasive methods for comparing the response of the left ventricle to a standardized stressful intervention in normal subjects and patients with heart disease. Accordingly, we evaluated the effects of sustained submaximal handgrip exercise on left ventricular wall motion, using radarkymographic video tracking for continuous analysis of the movement of selective segments of the left ventricular wall[1,2] in normal subjects and in patients with coronary artery disease. In addition, we assessed the influence of handgrip exercise on the external left heart dimension[3] and externally recorded systolic time intervals.

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TABLE I

Clinical Data in 12 Patients with Coronary Artery Disease

Case no.	Age (yr) & Sex	Time Since Infarct (mo.)	Electrocardiographic Site of Infarct	Wall Motion Abnormality	
				Type	Site
1	59F	8	Anteroseptal, apical	Hypokinesis	Apex
2	48M	24	Anteroseptal, inferior	Hypokinesis	Mid, low lateral, inferior
3	58M	19	Anteroseptal, inferior	Dyskinesis	Mid, low lateral, apex
4	38M	6	Anterior	Dyskinesis	Low lateral
				Hypokinesis	Apex
5	38M	2	Anterolateral	Dyskinesis	Apex
				Hypokinesis	Inferior
6	45M	30	Anterior, inferior	Dyskinesis	Mid, low lateral
				Hypokinesis	Inferior
				Asynchrony	Apex
7	30M	13	Anteroseptal, lateral	Dyskinesis	Low lateral, apex
				Hypokinesis	Mid lateral
				Asynchrony	Apex
8	62M	5	Inferior, apical	Hypokinesis	Low lateral, apex
9	53M	6	Anteroseptal, inferior	Hypokinesis	Apex
				Asynchrony	High, mid low lateral
10	73M	5	Anterolateral	Hypokinesis	High, mid low lateral, apex
11	67M	24	Inferior	Hypokinesis	Mid, low lateral, inferior
12	60M	22	Anterolateral	Dyskinesis	Low lateral, apex
				Hypokinesis	High lateral
				Asynchrony	Mid lateral

Methods

Case material: Twelve patients (mean age 53.5 years, range 30 to 73) with documented myocardial infarction but no history of angina pectoris and five subjects without cardiovascular disease (mean age 41.6 years, range 35 to 69) were studied in the supine basal state between 8:00 AM and 12:00 noon (Table I).

In six patients receiving digoxin, the last dose was taken 48 hours before study. On the day of study, none of these patients had evidence of cardiac decompensation such as tachycardia, pulmonary rales or a third heart sound. In all six patients, digoxin had been given for treatment of disorders occurring in association with acute myocardial infarction: transient atrial arrhythmias (four patients), mild left ventricular dysfunction (mean pulmonary capillary wedge pressure 15 mm Hg) (one patient) and pulmonary rales and quadruple rhythm (one patient). None of these patients subsequently had been limited by exertional dyspnea while taking digitalis. One of the six patients had received three 10 mg doses of propranolol before administration of this drug was discontinued 36 hours before study. This time span was chosen so that propranolol, which has a half-life of 3.2 hours after oral administration,[4] would be completely dissipated at the time of study. Propranolol had been instituted for therapy of ventricular premature contractions first noted 5 months after infarction. No patient had been receiving either quinidine or procainamide before study. A base-line scalar electrocardiogram was recorded; arterial blood pressure obtained by cuff sphygmomanometer and heart rate were monitored throughout the procedure. No patient had systemic arterial hypertension or electrocardiographic evidence of left or right bundle branch block.

Wall motion video tracking: This procedure was performed as previously described[2,5] using the commercially available Biotronix Heart Motion Video Tracker. The frequency response of this device, tested by means of a generated sine wave display, decreased to 75 percent of maximal response at a frequency greater than 15 to 16 Hz. With use of a 23 cm image intensifier, the fluoroscopic cardiac image was displayed on a Plumbicon television camera and recorded on video tape for later analysis or tracked directly during fluoroscopy. The analog video signal also was recorded on a Honeywell Visicorder photographic system for subsequent data analysis. After a standard inspiration, recordings were made of the left ventricular free wall at selected high, mid and low sites in the posteroanterior and left anterior oblique projections. Inferior and posterior wall movements were similarly recorded in the left anterior oblique and left lateral projections. In each patient the amplitude and velocity of wall motion were calculated at these selected sites before and after each intervention (Fig. 1). For each value of amplitude and velocity in each patient the average of at least three beats in which satisfactory recordings were obtained was used. Correction of these values for heart rate did not significantly alter them. Abnormal wall motion was defined according to a modification of the terminology of Herman and Gorlin[6]: Dyskinesis was defined as paradoxical systolic expansion; asynchrony as disturbance of the temporal sequence of contraction, early inward movement being followed by late paradoxical expansion or vice versa; and hypokinesis as diminished wall motion (Table I).

Measurements of systolic time intervals: These determinations were made from simultaneous recordings of a high-frequency phonocardiogram, the indirect carotid arterial pulse and the electrocardiogram on a multichannel recorder (Elena-Schonander Mingograf) at a paper speed of 100 mm/sec. Calculations of mean intervals were derived from measurements of 10 satisfactorily recorded car-

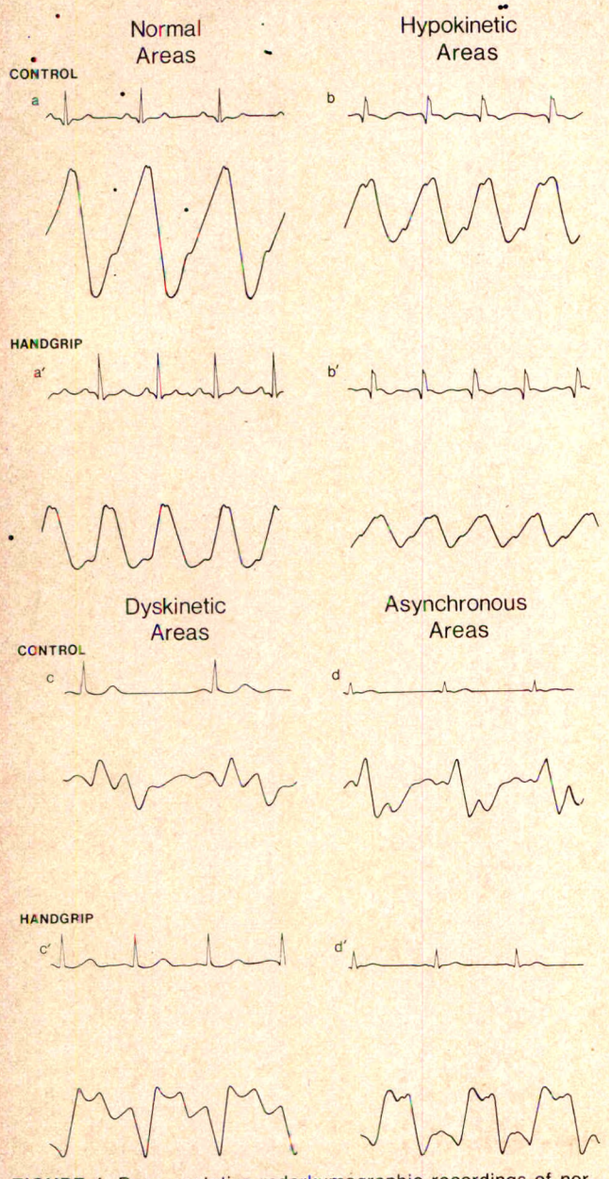

FIGURE 1. Representative radarkymographic recordings of normal **(a)**, hypokinetic **(b)**, dyskinetic **(c)** and asynchronous **(d)** areas of wall motion, before and during sustained handgrip exercise performed at a tension level of 15 percent of maximal voluntary contraction.

diac cycles. Observed time intervals were corrected for heart rate and sex according to the regression equations of Weissler et al.[7] and were expressed as indexes. The ratio of preejection period (PEP) to left ventricular ejection time (LVET) was obtained by dividing the observed preejection period by the uncorrected left ventricular ejection time since this ratio is independent of heart rate.[8]

Left heart dimension: This value was utilized as an index of left ventricular size[3] and was obtained by measuring the distance from the midline to the widest point on the left heart border on a standard chest roentgenogram exposed precisely at end-diastole by means of an electrocardiographic triggering device after a measured inspiration of 1,000 ml from functional residual capacity. It has previously been shown that the external left heart dimension correlates well with cineangiographic measurements of left ventricular cavity size.[3]

Isometric handgrip exercise: In the 12 patients and the 5 normal subjects control measurements were obtained of systolic time intervals, left heart dimension and amplitude and velocity of left ventricular wall motion at the selected sites indicated earlier. After giving informed consent, each subject was studied at the conclusion of a 3 minute period of sustained isometric handgrip exercise, performed at a tension level of 15 percent of the subject's previously determined maximal voluntary contraction, using a calibrated dynamometer.[9,10] In addition, 10 other normal subjects (mean age 34, range 25 to 42) had measurements of systolic time intervals before and at the end of a similar period of sustained handgrip exercise. Each patient was carefully instructed to avoid a Valsalva maneuver during the handgrip exercise.[10] No adverse effects such as angina pectoris or arrhythmias were noted during or after any of the studies.

Results

During handgrip, the average heart rate for the 12 patients increased by 18 percent from 63.8 ± 3.3 (standard error) to 75.4 ± 3.6 beats/min (P <0.001); in the 5 normal subjects, heart rate increased by 16.0 percent from 63.8 ± 5.2 to 74.0 ± 12.5 beats/min (P <0.01). In each patient systemic systolic arterial pressure increased by an average of 10 to 15 mm Hg during handgrip exercise.

Studies on left ventricular wall motion: In all 12 patients with coronary artery disease, some form of abnormal wall motion was observed in the base-line recording. In six patients who had sustained either isolated or combined anterior, lateral or apical infarction, areas of dyskinetic wall motion were recorded at those sites (Fig. 1c). In four patients prominent asynchrony was recorded, manifested by initial inward movement followed by early relaxation, and in three of these four a delayed paradoxical outward bulge followed the initial inward movement or vice versa (Fig. 1d). In 11 cases areas of hypokinesis were prominent (Fig. 1b).

Of nine patients who had either dyskinesis or asynchrony at rest, six demonstrated an increase in amplitude, and eight an increase in velocity of outward movement during handgrip. In three other cases, dyskinesis was produced de novo. For all of these nine patients the mean amplitude of outward dyskinetic movement increased during handgrip from 1.4 ± 0.31 to 2.2 ± 0.50 mm (68 percent increase, P <0.01) (Fig. 2), whereas mean velocity increased from 15.1 ± 2.7 to 18.4 ± 3.4 mm/sec (22 percent increase, P <0.05) (Fig. 3).

In initially hypokinetic areas observed in 11 patients, mean amplitude was reduced by 31 percent from 3.2 ± 0.42 to 2.2 ± 0.53 mm (P <0.01) and average velocity by 26 percent from 19.3 ± 3.1 to 14.2 ± 2.0 mm/sec (P <0.05) although an increased velocity was recorded in three patients (Fig. 2 and 3). Similarly, in areas of normal contraction noted in

each of the 12 patients, mean amplitude was reduced by 31 percent from 5.6 ± 0.53 to 3.9 ± 0.53 mm (P <0.01) and average velocity by 20 percent from 29.8 ± 3.9 to 23.9 ± 4.0 mm/sec (P <0.05) during handgrip (Fig. 2 and 3). However, in 3 of the 12 patients, velocity increased.

In the five normal subjects, the mean amplitude of wall motion was reduced by 34 percent from 6.3 ± 1.2 to 4.2 ± 0.3 mm (not significant), one subject demonstrating an increased amplitude. Mean velocity decreased by 51 percent from 57.4 ± 9.4 to 28.2 ± 2.02 mm/sec (P <0.05).

Studies on left ventricular size: Mean left heart dimension (uncorrected for body surface area) for all 12 patients increased during handgrip from 93.5 ± 12.6 (standard deviation) to 94.6 ± 13.2 mm (not significant); in the 5 normal subjects it decreased from 81.9 ± 2.67 to 79.5 ± 2.64 mm (P <0.05). However, in a subgroup of seven patients mean left heart dimension increased from 93.9 ± 14.4 to 97.7 ± 14.6 mm (P <0.005) while in the remaining five patients it decreased from 92.9 ± 10.5 to 90.26 ± 11.1 mm (P <0.01). Although initial heart size did not differ significantly in the two subgroups, in the seven patients whose left heart dimension increased wall motion abnormalities were notably more severe at rest, four displaying dyskinesis and the remaining three demonstrating severe diffuse hypokinesis or asynchrony, or both; in the five whose heart size decreased during handgrip, dyskinesis was observed in two and only mild hypokinesis was seen in the remaining three.

Studies on systolic time intervals: During handgrip mean preejection period index decreased in the 12 patients but this change was not significant (Fig. 4). There was no significant alteration in left ventricular ejection time index in the patient group. The average ratio of preejection period to left ventricular ejection time declined in the patient group, but this change was not significant.

In the 10 other normal subjects studied during handgrip exercise, mean preejection period index was unchanged (132.3 ± 4.6 to 131.1 ± 3.7 msec), 4 of the 10 values increasing, whereas left ventricular ejection time index increased in all cases, from a mean of 408.0 ± 4.0 to 422.1 ± 5.1 msec (P <0.001) (Fig. 4). Mean ratio of preejection period to left ventricular ejection time was reduced by 10 percent from 0.357 ± 0.013 to 0.323 ± 0.013, a change which was not significant since the same four subjects whose preejection period index rose after handgrip showed an increased value.

Discussion

Previous investigations of the effects of stressful interventions on the left ventricle have utilized measurements requiring invasive techniques such as cardiac catheterization. For example, abnormal left ventricular function curves have been observed in patients with coronary artery disease in response to sustained isometric handgrip exercise,[11] and atrial

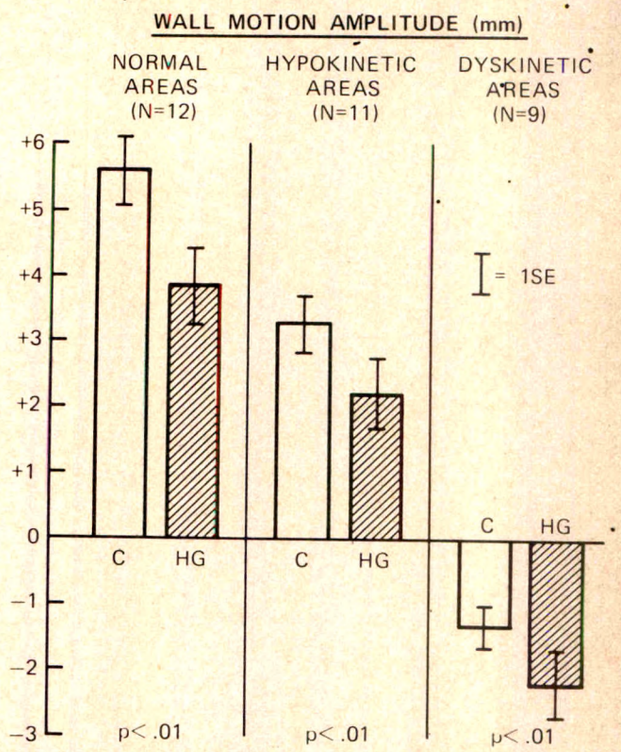

FIGURE 2. Average wall motion amplitude of normal and abnormal areas during control (C) measurements, and during sustained handgrip (HG) exercise. 1SE indicates 1 standard error of the mean.

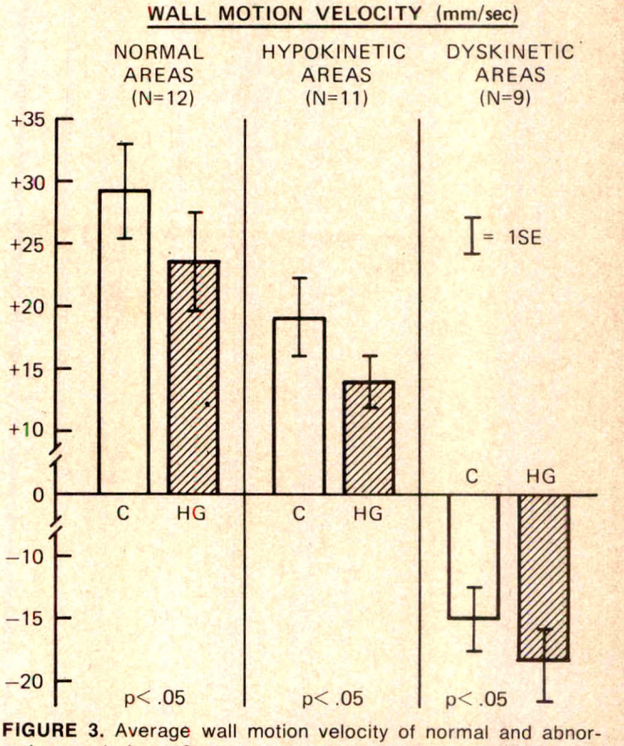

FIGURE 3. Average wall motion velocity of normal and abnormal areas before (C) and during sustained handgrip (HG). 1SE indicates 1 standard error of the mean.

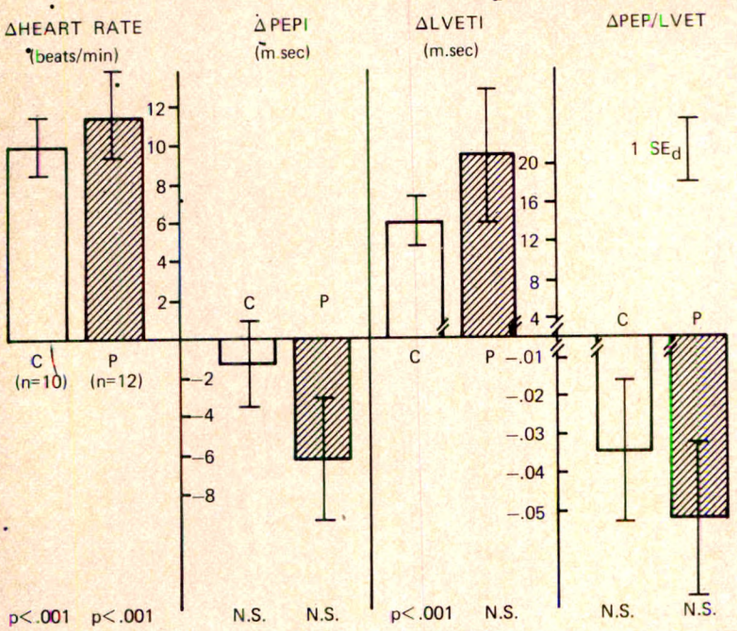

FIGURE 4. Changes (Δ) in heart rate, preejection period index (PEPI), left ventricular ejection time index (LVETI), and PEP/LVET during sustained handgrip in the 10 normal control subjects (C) and in the 12 patients (P). N.S. = not significant; SE_d indicates the standard error of the difference.

pacing during cardiac catheterization has been used to induce or exacerbate dyskinesis as evaluated by left ventriculography.[12] In this study we used three totally noninvasive methods, radarkymographic video tracking, measurement of the left heart dimension and calculation of systolic time intervals in order to assess the response of the left ventricle to a standardized stressful intervention in normal subjects and in patients with previous myocardial infarction.

Changes in wall motion: The results utilizing radarkymographic video tracking revealed that the normal response to submaximal isometric handgrip exercise is a reduction in both the amplitude and velocity of left ventricular wall motion. This reduction was observed in all locations in the normal subjects as well as in areas of normal wall movement in the patients with previous myocardial infarction. However, the response to handgrip in initially abnormal areas of wall motion was quite different. In six of nine patients the amplitude of initially paradoxical wall motion increased and, in three others, dyskinesis appeared de novo. These observations differ somewhat from those of Flessas et al.,[13] who noted only hypokinesis by cineangiography during handgrip in 8 of 10 patients with coronary artery disease. Our results correlate with the frequently observed appearance or accentuation of atrial gallop sounds[14,15] and the development of palpable precordial dyskinesis[15] during or after handgrip exercise. On the basis of these observations, serial noninvasive evaluation of dyskinetic areas after a standardized, stressful intervention is now possible. Prospective assessment of such areas before and after drug therapy and coronary revascularization procedures should provide useful information on the efficacy of such treatment.

Changes in left heart dimension: The normal response of the left heart dimension to handgrip exercise performed at a tension level of 15 percent of maximal voluntary contraction appears to be a reduction in heart size; this reduction was seen in all five control subjects. In the patients with coronary artery disease, the changes in heart size were variable. In the seven patients whose left heart dimension increased during handgrip, wall motion abnormalities were more severe and diffuse at rest and control heart size was slightly greater than in the five patients whose left heart dimension decreased. These observations suggest that in patients with severe wall motion abnormalities heart size tends to increase in response to isometric stress. This reaction is abnormal and may serve to increase myocardial oxygen consumption even further in these patients.

Mechanism of changes in left ventricular wall motion and size: Previous studies have indicated that the overall response to isometric exercise is complex and variable, depending in part on the age and cardiovascular status of the subject, and particularly on the level of tension maintained.[9,10,16] During handgrip performed at a tension level of 15 percent of maximal voluntary contraction, there is a progressive but slow increase in blood pressure, cardiac output and heart rate. Upon release of handgrip these measurements promptly return to control levels. At 20 to 30 percent of maximal voluntary contraction, blood pressure, cardiac output and heart rate continue to increase steadily during handgrip; upon release, these variables increase further.[9,10] Therefore, to prevent excessive myocardial oxygen

demand, we used a tension of 15 percent of maximal voluntary contraction.

At the level of submaximal handgrip exercise used in this study, there is little change in systemic vascular resistance or stroke volume in younger subjects. However, in older subjects, especially in those with cardiovascular disease, a significant increase in systemic vascular resistance[16] and a decrease in stroke volume is often observed. Each level of tension produces a different "steady state"; hence, minor differences in the fraction of maximal voluntary contraction maintained will produce significant differences in the degree to which these physiologic variables are affected. These considerations help to explain the variability of the observed changes in wall motion, heart size and systolic time intervals.

Thus, the wall motion changes induced by handgrip exercise in patients with coronary artery disease are the net result of several influences: (1) augmented myocardial contractility, mediated by the sympathetic nervous system[17]; (2) increased systemic vascular resistance, especially in older patients (these two factors result in increased intraventricular systolic pressure and increased outward distending force acting on the critical area) and; (3) increased myocardial oxygen consumption, presumably mediated by changes in systemic arterial pressure, heart rate and adrenergic influences.

The reduction in wall motion amplitude in normal areas that we observed during handgrip may simply be the result of decreased stroke volume and stroke excursion associated with tachycardia produced by the maneuver. Variable changes in heart size might also be expected after handgrip exercise for similar reasons, depending on the relative contributions made by sympathetic stimulation and increased systemic vascular resistance. These responses, particularly the latter, vary greatly from patient to patient.[9,10]

Systolic time intervals as index of left ventricular function: There is little information on the effect of sustained submaximal isometric handgrip exercise on systolic time intervals in patients with documented coronary artery disease. In our patients both preejection period index (PEPI) and the PEP/LVET ratio decreased during isometric exercise. However, the results were not uniform since increases in preejection period index occurred in four patients and a rise in the PEP/LVET ratio was observed in five patients. A similar variability was noted in the normal control subjects and is in accord with the observations of Frank and Haberern,[18] who concluded that left ventricular ejection time shortens with mild to moderate increase in arterial pressure and lengthens when the arterial pressure increases further. The inconsistent changes in left ventricular ejection time index, preejection period index and PEP/LVET observed in some of our patients are compatible with the wide spectrum of physiologic responses to handgrip mentioned previously. This is particularly true of the role of alterations in systemic vascular resistance and adrenergic influences reported by others in both normal and abnormal subjects.[9,10,17] Although mild or supine or upright exercise can induce abnormalities in systolic time intervals in patients with coronary artery disease, analyses of the changes in such intervals comparing rest with exercise using each patient as his own control have failed to provide an improved separation of patients with normal and those with abnormal hemodynamics.[19] Moreover, McConahay et al.[19] could not predict reliably minor abnormalities of left ventricular function in individual patients with coronary artery disease.

Our results differ somewhat from those recently reported by Siegel et al.,[15] who observed no significant alterations in preejection period index or PEP/LVET in patients with coronary artery disease undergoing maximal handgrip exercise. Thus, although systolic time intervals may not be useful in detecting minor abnormalities in left ventricular function at rest or after isotonic or isometric exercise, we have previously demonstrated[20] that serial assessment of such intervals in the same patient correlates well with changes in clinical status and in some instances may even precede deterioration of left ventricular function. Whether serial studies of systolic time intervals during isometric exercise stress in patients with coronary artery disease will prove useful requires further investigation.

Possible influence of previous drug therapy: Finally, the possible influence of previous drug therapy on our results requires consideration. Of the three patients who developed dyskinesis de novo, one was receiving no medication and two had been receiving digoxin. Of the seven patients whose left heart dimension increased, four had been taking digitalis and three had not. Of the five patients whose left heart dimension decreased during handgrip exercise, one had been receiving propranolol and digoxin, two had been taking digoxin alone and two had been receiving no medication. Two of the four patients who had an increased PEP/LVET ratio during handgrip exercise were receiving digoxin; in the eight patients who had a decrease in this ratio, four had received no prior medication, three had been taking digoxin and one digoxin and propranolol. Although it is likely that heart size, systolic time intervals and abnormalities of left ventricular wall motion would tend to be altered by acute congestive cardiac failure, all our patients appeared to have good compensation both clinically and hemodynamically at the time of study. Thus, previous medication appeared to produce no consistent effects, and our results can be attributed directly to the intervention of isometric handgrip exercise.

Acknowledgment

We are indebted to Dr. John Ross, Jr. for his helpful comments and to Mr. Joseph Byrne for expert technical assistance.

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Enhanced Left Ventricular Performance with Phentolamine in Acute Myocardial Infarction

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The hemodynamic effects of phentolamine (Regitine) were evaluated in nine patients with increased left ventricular filling pressure and clinical left ventricular failure (Group A) and five patients with normal left ventricular filling pressure and an uncomplicated course (Group B) within 48 hours of an acute myocardial infarction. Decreased afterload was noted in both groups after administration of phentolamine. Improved left ventricular performance was noted only in Group A and was manifested by a decrease in left ventricular filling pressure (from 23.9 to 13.6 mm Hg), increase in cardiac index (from 2.1 to 2.9 liters/min per m^2), increase in stroke volume index (from 22.5 to 29.3 cc/beat per m^2), and little change in heart rate (from 94.2 to 99.8 beats/min). In contrast, a decrease in stroke volume index (32 to 26 cc/beat per m^2) and a greater increase in heart rate (77 to 94 beats/min) were noted in Group B. Reduction of preload, which accompanies a reduction in afterload with administration of phentolamine, may have caused a greater decrease in end-diastolic volume in Group B, resulting in the reduced stroke volume index and compensatory increase in heart rate. Our findings suggest that afterload reduction induced by administration of phentolamine enhances depressed left ventricular function in patients with increased left ventricular filling pressure after myocardial infarction. Careful monitoring to prevent complications is required.

Treatment of impaired left ventricular function after an acute myocardial infarction often presents a therapeutic dilemma. Traditionally, severe left ventricular dysfunction, manifested by decreased cardiac output or pulmonary venous congestion, or both, has been treated with inotropic or diuretic agents. Inotropic agents such as digitalis have been reported to cause little change in cardiac hemodynamics in acute infarction,[1,2] and recent experimental data suggest that they may increase the area of myocardial ischemia.[3] Diuretic agents, although effective in reducing pulmonary venous congestion, do not enhance left ventricular performance.[4]

Agents that reduce afterload have significant effects on ischemic heart disease. Thus, sodium nitroprusside, an agent that causes peripheral vasodilatation, has enhanced left ventricular performance in patients with acute myocardial infarction,[5] and phentolamine (Regitine®), which also reduces afterload, has been reported effective in treating chronic refractory heart failure.[6] Phentolamine has also been said to have a positive inotropic effect that might be beneficial in some circumstances. In this study we evaluated the hemodynamic effects of phentolamine in acute myocardial infarction to assess the potential clinical application of this drug.

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TABLE I

Hemodynamic Effects of Phentolamine in Acute Myocardial Infarction in Nine Patients (Group A) with Increased Left Ventricular Filling Pressure and Five Patients (Group B) with Normal Left Ventricular Filling Pressure

Case no.	Age (yr) & Sex	HR		MAP		MPAP		LVFP		CI		SVI		SWI		SVR		PVR	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Group A																			
1	59M	84	82	112	80	25	13	22	8	2.20	2.76	26.2	33.6	42.3	38.7	2080	1232	100	48
2	60F	98	94	120	110	29	25	20	11	1.75	2.11	17.8	25.4	34	40.3	3160	2630	758	547
3	59M	110	108	113	83	32	21	25	16	2.96	5.04	27	47	34	45	1377	639	96	40
4	73M	78	76	85	57	30	19	24	16	1.69	2.14	21.6	28.2	26.4	23.1	2585	1373	916	457
5	63M	118	118	73	62	30	25	24	20	2.70	3.30	23	28	24	25	1214	845	498	340
6	60M	73	98	110	69	26	15	19	6	2.46	3.97	34	41	53	41	1734	682	86	53
7*	51M	117	143	109	72	54	34	45	26	2.11	3.40	18	24	29	25	2033	836	1007	395
8*	67M	94	100	81	67	26	17	16	5	1.74	1.96	18.5	19.6	21.3	18.9	1980	1464	640	372
9	69F	76	80	86	72	28	24	20	14	1.21	1.34	16	17	15	14	3565	2692	166	187
Mean		94.2	99.8	98.8	74.7	31.1	21.4	23.9	13.6	2.1	2.9	22.5	29.3	31.0	30.1	2192	1377	474	271
± SEM		±5.8	±7.0	±5.7	±5.1	±3.0	±2.1	±2.8	±2.3	±0.2	±0.4	±1.9	±3.2	±3.8	±3.7	±260	±262	±124	±63
P value		NS		0.0005		0.0005		0.005		0.005		0.005		NS		0.0005		0.0005	
Group B																			
10	55M	75	114	95	90	12	...	8	5	2.7	3.4	36	29	49	37	1514	1142	102	...
11	70F	78	98	92	73	21	12	14	7	1.97	2.07	25	21	33	22	2062	1609	174	118
12	70M	66	70	97	75	18	12	12	8	1.89	1.79	28	21	40	28	2028	1706	137	96
13	42M	74	98	99	97	13	12	9	4	3.2	3.4	43	34	56	46	1320	1218	53	50
14	59M	94	90	85	78	14	11	11	6	2.7	2.4	29	27	31	28	1416	1395	50	93
Mean		77	94	94	83	16	12	11	6	2.5	2.6	32	26	42	32	1668	1414	103	89
± SEM		±4.6	±7.1	±2.4	±4.6	±1.7	±0.2	±1.1	±0.7	±0.25	±0.33	±3.2	±2.5	±4.7	±4.2	±157	±109	±24	±14
P value		0.05		0.05		0.05		0.005		NS		0.005		0.005		0.02		NS	

* Patients 7 and 8 were the only nonsurvivors.

CI = cardiac index (liters/min per m²); HR = heart rate (beats/min); LVFP = left ventricular filling pressure (mm Hg); MAP = mean arterial pressure (mm Hg); MPAP = mean pulmonary arterial pressure (mm Hg); NS = not significant; Post = after administration of phentolamine; Pre = before administration of phentolamine; PVR = peripheral vascular resistance (dynes sec cm^{-5}); SEM = standard error of the mean; SVI = stroke volume index (cc/m²); SVR = systemic vascular resistance (dynes sec cm^{-5}); SWI = stroke work index (g-m/beat per m²).

Material and Methods

Fourteen studies were performed in 13 patients (3 women and 10 men, aged 42 to 73 years) with historical, electrocardiographic and laboratory evidence of an acute myocardial infarction within 48 hours of the onset of symptoms (Table I). Infarction was located in the anterior wall in nine patients and in the inferior wall in three; an additional patient had only historical and enzyme evidence of acute myocardial infarction. Two patients had cardiogenic shock at the time of the study, nine had clinical manifestations of left ventricular failure with physical and radiologic signs of pulmonary venous congestion, and four had clinically uncomplicated infarction. One patient (Cases 3 and 14, Table I) was studied twice, once when he had signs of pulmonary venous congestion and again when he was free of congestion. Phentolamine was administered intravenously by a constant infusion pump (Harvard) over a 1 hour period in all patients. A dose of 5 mg was administered in the first minute; then an infusion rate was selected that would decrease left ventricular filling pressure significantly or reduce mean arterial pressure by approximately 20 mm Hg. In several mildly hypotensive patients the initial bolus dose was not given. The actual infusion rate ranged from 0.1 to 2 mg/min; the usual rate required was 0.5 to 1 mg/min. After control measurements were obtained, data were recorded 5, 15, 30 and 60 minutes after infusion.

Arterial pressure (AP) was measured directly through a 20 gauge cannula inserted in the radial artery. Right atrial (RA), pulmonary arterial (PA) and pulmonary capillary wedge (PCW) pressures were recorded at the bedside through a balloon-tipped triple lumen catheter. Cardiac output (CO) was measured by the thermodilution technique with the same catheter.[8]

Derived hemodynamic variables were calculated as follows: stroke volume index (SVI) = SV/BSA (cc/m^2); stroke work index (SWI) = SVI × $\overline{AP}$ × (0.0144) (g-m/m^2); systemic vascular resistance (SVR) = 80($\overline{AP}$ − RA)/CO (dynes sec cm^{-5}); and pulmonary vascular resistance = ($\overline{PA}$ − PCW/CO) × 80 (dynes sec cm^{-5}) where SV = stroke volume, BSA = body surface area and 0.0144 and 80 are conversion factors.

Results

The hemodynamic results in all patients are summarized in Table I. The post-phentolamine values listed represent the maximal response to the drug. These responses were usually observed after administration of the first 5 mg dose and were then maintained over the 1 hour period of infusion. In several cases the initial response was assessed as inadequate, and the infusion rate was increased until an adequate response was elicited.

The response in all 14 studies in the 13 patients was characterized by a decrease in left ventricular filling pressure, mean arterial pressure and systemic and pulmonary vascular resistance levels. However, improved left ventricular performance was noted only in patients whose left ventricular filling pressure (pulmonary capillary wedge or pulmonary arterial end-diastolic pressure) was initially increased. Nine patients had an initial left ventricular filling pressure greater than 15 mm Hg and were classified in Group A. They demonstrated an increase in stroke volume with a concomitant significant decrease in left ventricular filling pressure (Fig. 1). Cardiac index increased in all nine patients. In seven of these nine patients there was no significant change in heart rate.

In two patients, who also had the greatest decrease in mean arterial pressure, heart rate increased by 25 and 26 beats/min, respectively. The changes noted in calculated stroke work index were not consistent because of the variable decrease in mean arterial pressure. In contrast, although the five patients with a normal initial left ventricular filling pressure (Group B) also showed a reduction in left ventricular filling pressure, the stroke volume was reduced during drug infusion (Fig. 1). An increase in heart rate was also noted in four of these five patients.

Discussion

Our study demonstrates that effective left ventricular performance can be significantly improved by administration of phentolamine in patients with depressed left ventricular function and pulmonary vascular congestion due to an acute myocardial infarction. This improvement was indicated by prompt re-

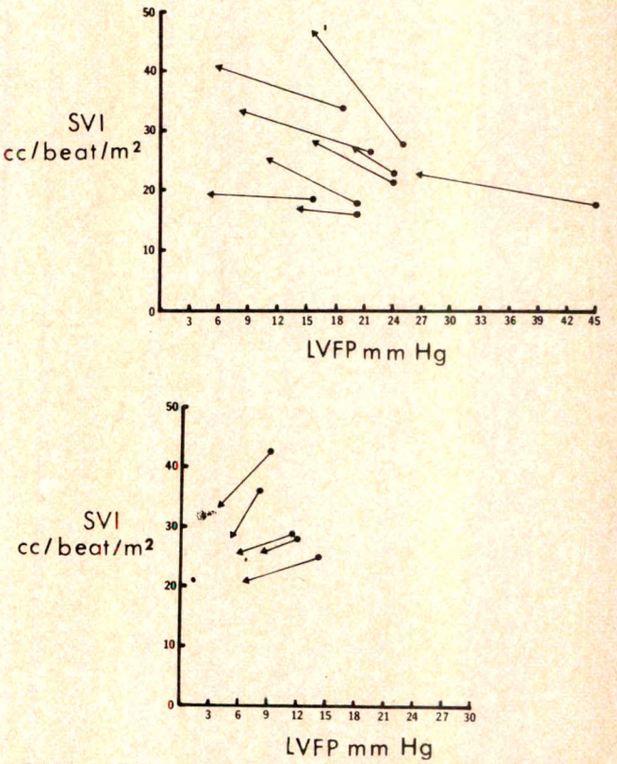

FIGURE 1. Effect of afterload reduction with phentolamine in nine patients with increased left ventricular filling pressure (LVFP) (**top panel**) and five patients with normal filling pressure (**bottom panel**) after acute myocardial infarction. An increase in stroke volume index (SVI) (mean change 6.8 cc [+30 percent]) and decrease in left ventricular filling pressure (mean change 10.3 mm Hg) was noted in all patients with an initially increased filling pressure. In contrast, all patients with an initially normal filling pressure had a further decrease in this variable (mean change 4.8 mm Hg) and an associated decrease in stroke volume index (mean change 6 cc [−18 percent]).

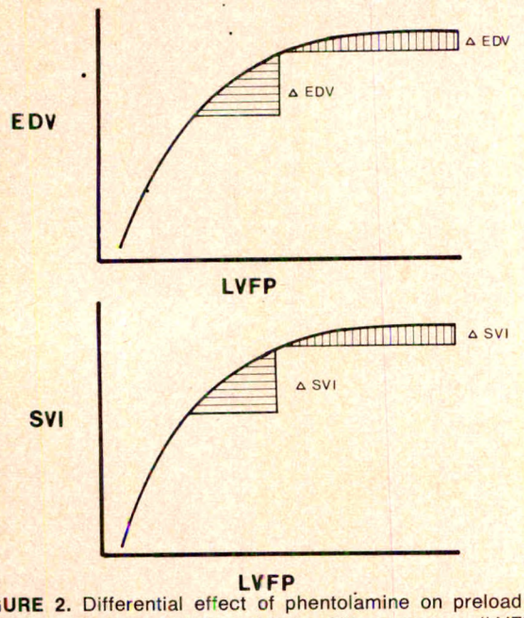

FIGURE 2. Differential effect of phentolamine on preload with normal and increased left ventricular filling pressure (LVFP): a hypothesis. Left ventricular compliance, shown in the **top panel** as end-diastolic volume (EDV) on the vertical axis and left ventricular filling pressure on the horizontal axis, is assumed to be equal for both groups and unchanged by pharmacologic intervention. Reduction of an increased filling pressure to normal (**vertical bars**) is associated with a minimal change in end-diastolic volume with a resultant minimal change in stroke volume index (SVI). In contrast, decrease of a normal filling pressure to a lower value (**horizontal bars**) is associated with a much larger decrease in end-diastolic volume and a concomitant large decrease in stroke volume index. This greater reduction in stroke volume index may be sufficient to counterbalance any increase in this variable due to an increased ejection fraction associated with afterload reduction.

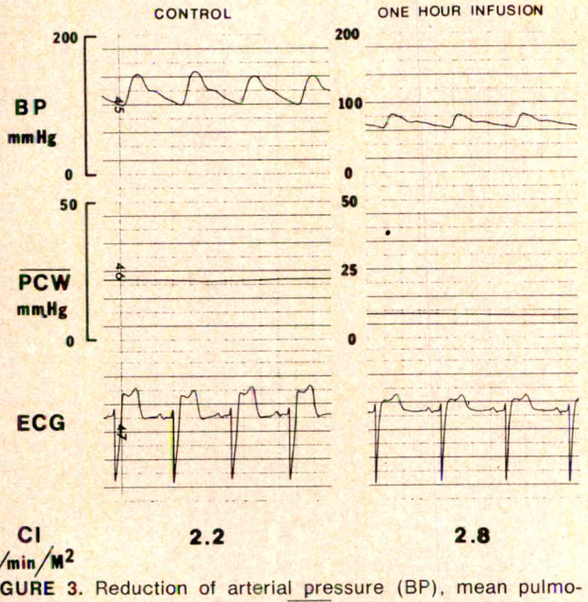

FIGURE 3. Reduction of arterial pressure (BP), mean pulmonary capillary wedge pressure ($\overline{PCW}$) and current of injury on the electrocardiogram (ECG) during phentolamine infusion in acute myocardial infarction. CI =. cardiac index.

duction in left ventricular filling pressure and a concomitant increase in stroke volume. The reduction in left ventricular filling pressure was probably related both to an increase in venous capacitance[9] and to an increase in ejection fraction due to the reduced afterload. Similar improvement in left ventricular performance has been reported after administration of nitroprusside.[5] However, in our patients with normal left ventricular filling pressure, administration of phentolamine resulted in reduced stroke volume, concomitant tachycardia and a further decrease in left ventricular filling pressure.

Mechanisms of hemodynamic effects of phentolamine: The precise mechanism of these disparate hemodynamic responses is not clear, but the interaction of changes in afterload and preload may be partly responsible (Fig. 2). Reduction in afterload decreases impedance to left ventricular ejection, which in turn increases stroke volume. In contrast, reduction in preload to values substantially less than 15 mm Hg decreases stroke volume as a result of shorter end-diastolic fiber length. In our study changes in end-diastolic volume could not be measured directly and could only be inferred from the measured changes in left ventricular diastolic pressure, extrapolated to the curvilinear relation between left ventricular diastolic pressure and volume.[10] In the presence of increased left ventricular end-diastolic pressure, a reduction in preload to 15 mm Hg will presumably cause only a small decrease in diastolic volume, and the reduction in stroke volume due to decreased preload will be small. The concomitant reduction in left ventricular impedance caused by phentolamine may therefore result in a significant increase in stroke volume. In contrast, if left ventricular filling pressure is initially normal, a further reduction of this variable is associated with a greater decrease in end-diastolic volume. In turn, this decrease may cause a reduction in stroke volume, which may be greater than the increase expected from reduction of afterload. The net result may be reduction in stroke volume with a compensatory increase in heart rate.

Other pharmacologic effects of phentolamine: Although the major factors in the hemodynamic improvement noted appear to be related to the interactions between altered afterload and preload, other pharmacologic effects of phentolamine may also be active. Enhanced release of insulin or reversal of catecholamine-induced suppression of insulin, which may enhance aerobic myocardial metabolism, has been described.[11] Inhibition of the bronchoconstriction noted after administration of histamine has been documented and may decrease airways resistance noted during periods of left ventricular failure.[12] Several investigators have claimed that phentolamine has a direct positive inotropic effect on the heart. However, Rabinowitz et al.[13] in a recent study utilizing the isolated cat papillary muscle, demonstrated no direct positive inotropic effect of phentolamine on the myocardium and found no evidence of

an indirect effect produced by release of catecholamines. They also noted that phentolamine had no effect on the adenyl cyclase activity of the myocardium, suggesting that there were no direct effects on the beta receptor. Nevertheless, the tachycardia produced in some of our patients suggests that there was a reflex increase in sympathetic tone, related to a reduction in intravascular pressure.

Clinical implications: The documented immediate improvement in left ventricular pump function in patients with acute myocardial infarction after administration of phentolamine has potential long-term benefits. Reduction in both preload and afterload without change in heart rate or inotropic state should result in a decrease in myocardial oxygen demand. Such an effect could reduce ultimate infarct size and, by relieving myocardial ischemia in peripheral zones, further improve ventricular performance. In one of our patients a decreased amplitude of the current of injury on the electrocardiogram was noted after 60 minutes of phentolamine infusion (Fig. 3) although it cannot be stated whether this was related to the effect of phentolamine or was coincidental. However, recent experimental data have demonstrated that in the depressed, infarcted heart an increase in afterload exacerbates ischemic injury.[14] The electrocardiographic changes we observed are consistent with these data.

Precautions during phentolamine infusion: Because our study was designed to assess the short-term hemodynamic effects of phentolamine in acute myocardial infarction, serial hemodynamic measurements were not carried out beyond 1 hour. However, in two patients infusion was continued beyond 1 hour and, in both patients, periodic adjustment of the infusion rate was required to maintain the hemodynamic response. The dose of phentolamine was then gradually reduced, and the drug was discontinued as base-line hemodynamics and clinical status improved. There was no evidence of tachyphylaxis or delayed adverse response.

Although no adverse reactions occurred after administration of phentolamine in our patients, it is pertinent to note that our studies were performed in a setting in which it was possible to monitor left ventricular filling pressure, systemic arterial pressure and cardiac output. Since patients with a normal left ventricular filling pressure derive no benefit from afterload reduction, it is mandatory to measure this variable before administering drugs that may decrease afterload. Careless administration of such agents may reduce arterial pressure precipitously to a level at which adequate coronary perfusion might not be maintained. In such circumstances, left ventricular function may be seriously depressed as a result of increased myocardial ischemia. Continuous monitoring of left ventricular filling pressure and arterial pressure is thus a prerequisite for determining the appropriate rate of administration of these afterload-reducing agents; otherwise an apparently beneficial therapeutic agent may turn out to be a hazardous one.

Acknowledgment

We acknowledge with thanks the technical assistance of Docela Edwards, Luciann Robinson, Jacques Balian, Roman Kulczycky, Alma Alredge, Lance LaForteza and Sharman Jamison.

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Results of Aortocoronary Artery Saphenous Vein Bypass Surgery for Ischemic Heart Disease

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The results of direct myocardial revascularization using aortocoronary artery saphenous vein bypass grafting in 100 consecutive patients with ischemic heart disease are evaluated. Twelve patients died at operation or early thereafter. Of 88 patients surviving, 72 had severe angina pectoris before operation, 15 had moderate angina and 1 mild angina. After operation, only 10 patients had severe angina, 6 had moderate angina and 72 were free of angina. Thirty-seven patients underwent an exercise stress test in the upright position using a bicycle ergometer 3 to 5 days before operation. Angina pectoris developed in 33 patients during exercise and was accompanied by significant S–T segment depression. The exercise study was terminated in four patients who experienced shortness of breath. Three to four months postoperatively, 20 of these 37 patients underwent exercise at similar and higher work load levels. No pain or S–T segment depression was noted in 18 of the 20 patients. Two of the 20 patients had positive exercise responses similar to their preoperative responses. Seventeen of the 37 patients did not undergo exercise testing after operation: Four died; eight showed clinical improvement but were not available for repeat exercise studies; the remaining five showed no clinical improvement and did not undergo repeat exercise studies.

Left ventricular function was determined by measuring ejection fraction and mean velocity of circumferential fiber shortening per circumference in 51 patients. The preoperative ejection fraction of patients who manifested clinical improvement after operation was greater than that of patients whose condition did not improve; however, there was considerable overlap of data.

The success or failure to achieve a good clinical result correlated with flow through the bypass, measured at the time of operation. Flow through the saphenous bypass was directly related to the state of the distal coronary arterial system.

Direct myocardial revascularization by aortocoronary artery saphenous vein bypass grafting has been developed successfully by Favaloro et al.,[1] Johnson et al.[2] and others[3–7] in the past several years. This method of direct myocardial revascularization has gained wide acceptance and is being used in many medical centers. Regrettably, since the reported clinical results have not been analyzed in detail, the criteria for selection of patients are not well established.

This report describes (1) clinical results of coronary artery bypass surgery immediately and 4 to 12 months after operation, (2) determination of flow established through the bypass graft and the relation of flow to the status of the distal coronary arteries determined by coronary arteriography, and (3) determination of left ventricular function before surgery and its relation to the clinical results after coronary artery bypass surgery.

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Clinical Material and Methods

From April to October 1971, a total of 100 consecutive patients received single or multiple aortocoronary artery bypass vein grafts at the Hahnemann Medical College and Hospital. There were 88 men, whose ages ranged between 31 and 65 years (average age 49 years). The 12 women were 38 to 65 years of age (average age 52 years). Before operation, all patients were evaluated clinically and subjected to left heart hemodynamic studies including left cineventriculography and selective coronary cinearteriography. Angina pectoris was the most prominent and frequent symptom, and was graded mild, moderate or severe. Angina was considered mild if it occurred with severe and vigorous effort, moderate if it occurred during routine and sedentary activities, and severe when it occurred with minimal effort or at rest. The patients with severe angina did not respond satisfactorily to medical therapy, and aortocoronary bypass surgery was performed. Those with mild or moderate angina were subjected to surgery on the basis of significant obstructive lesions demonstrated by coronary arteriography.

Left ventricular function was determined from the left cineventriculogram. Ejection fraction[8] and mean velocity of circumferential fiber shortening per circumference[9] were also measured in 51 patients. The left ventriculogram was obtained in the right anterior oblique projection. The silhouette of the left ventricular cavity was drawn in outline at the end of diastole and at the end of systole. The long axis of the left ventricle was measured from the aortic cusp to the left ventricular apex. The minor diameter of the left ventricular circumference was measured from each outline drawing perpendicular to and at the midpoint of the long axis. The left ventricular end-diastolic and end-systolic volumes were calculated by the following formula:

$$\pi/6 \times L \times D^2(CF)^3$$

where L is long axis, D is the minor diameter and CF is the X-ray magnification factor. Stroke volume was found by subtracting end-systolic from end-diastolic volume. The ejection fraction was calculated from the systolic volume divided by the end-diastolic volume. The mean velocity of circumferential fiber shortening per circumference at the minor diameter was calculated by the following formula and is expressed in centimeters per seconds:

$$\pi D - \pi D_1/SEP \times \pi D \text{ or } D - D_1/SEP \times D$$

where SEP is the systolic ejection period and D_1 is the minor diameter at end-systole. The cine magnification factor was obtained from the image of the Lehman catheter diameter divided by the actual diameter of the catheter. The coronary arteriograms were obtained by the Sones technique. Distal runoff was termed good when the distal arteries beyond the major proximal obstructive lesions appeared normal or showed only minimal luminal irregularities. Distal runoff was termed poor when the lumen of the distal arteries beyond the major proximal obstructive lesions was compromised by at least 30 percent or more, with significant diffuse luminal narrowing.

Graded exercise stress tests were performed by 37 patients in an upright position using a bicycle ergometer. Each patient started at a work load of 25 watts; every three minutes the work load was increased by 25 watts. The patients rested for 10 minutes after each six minute exercise period. Exercise was terminated with the occurrence of (1) chest pain associated with S–T segment depression of at least 0.5 cm, or (2) severe shortness of breath. After operation, 20 of these patients underwent repeat exercise tests performed in the same manner.

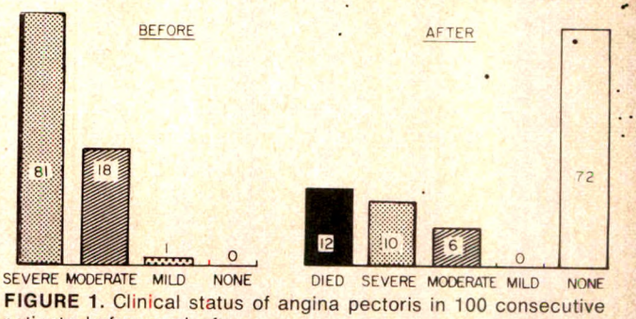

FIGURE 1. Clinical status of angina pectoris in 100 consecutive patients before and after aortocoronary artery saphenous vein bypass graft surgery.

The graft blood flow at operation was measured with a North Carolina electromagnetic flowmeter in 86 aortocoronary grafts in 50 patients. The measurements were made at the termination of cardiopulmonary bypass and at least 5 to 10 minutes after stabilization of blood pressure and heart rate. All patients had sinus rhythm. The probes were precalibrated by means of both blood and saline solution flowing through a segment of the femoral artery of a dog. The size of the probes used was determined by the size of the bypass vein graft. Average flow was calculated from at least two measurements from each bypass.

Results

Clinical Response: Angina Pectoris

The effects of aortocoronary artery saphenous vein bypass grafting on angina pectoris are shown in Figure 1. Of the 88 patients who survived operation, 72 became symptom-free. The patients were classified in five groups to permit further analysis of the results of surgery in relation to the number of vessels diseased and bypassed (Fig. 2).

Group I: In this group (14 patients) with single vessel disease and one bypass, all survived. Angina

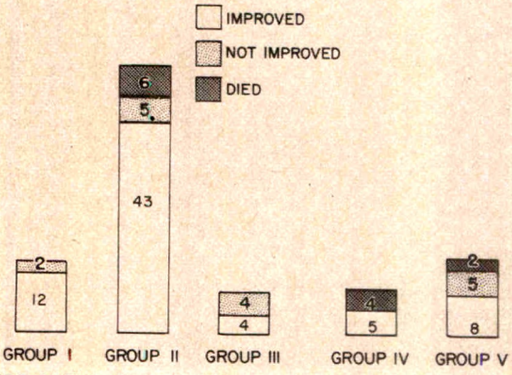

FIGURE 2. The effect of aortocoronary artery bypass surgery in 100 patients, according to the number of vessels diseased and bypassed. Group I = one vessel disease and one bypass graft; Group II = two vessel disease and two bypass grafts; Group III = two vessel disease and one bypass graft; Group IV = three vessel disease and three bypass grafts; Group V = three vessel disease and two bypass grafts.

TABLE I

Results of Aortocoronary Artery Saphenous Vein Bypass Surgery in 100 Cases

		Myocardial Infarction		Relief of Angina
	no.	Early	Late	
Patients who died	12	7	...	...
At operation	3	0	...	...
In early postoperative period (24 hours)	7	5	...	...
In late postoperative period (5–11 days)	2	2	...	...
Survivors	88	10	2	72 (82%)

pectoris was not alleviated in two patients, both women; both had occlusion of the graft and deterioration of ventricular function, as shown by postoperative cineangiography. In both women, the bypass was made to the left anterior descending coronary artery and there was good distal runoff. The flow through the graft in one patient was 160 cc/min. Of the remaining 12 patients in this group whose condition improved, 8 had a single bypass to the left anterior descending artery, 1 had a bypass to the circumflex artery and 3 had a bypass to the right coronary artery.

Group II: In this group of 54 patients with two vessel disease and two bypasses, 5 patients had no alleviation of angina and all 5 had poor distal runoff postoperatively. One of these five patients had an acute anteroseptal myocardial infarction 4 weeks after operation. Upon restudy, we found that the proximal obstructive lesion of the left anterior descending artery had progressed to complete occlusion and that the bypass graft to the vessel was also occluded. In this group of 54 patients, 6 died, 3 in the operating room after prolonged cardiopulmonary bypass and 2 within 24 hours because of massive myocardial infarction; 1 died 5 days after operation. Autopsy study showed that the latter patient had an occlusion of the graft to the left anterior descending coronary artery. The three patients who died after operation had poor distal runoff demonstrated by arteriography.

Group III: In this group of eight patients with two vessel disease but only one bypass, bypass to the other artery could not be accomplished because of diffuse disease involving its distal portion. Four patients manifested clinical improvements, and four did not. The four patients without angina had good distal runoff. The four patients who continued to experience angina had poor distal runoff of the bypassed vessel.

Group IV: Of this group of nine patients with three vessel disease and three bypasses, four patients died, one in the operating room after prolonged bypass, and three from postoperative acute anteroseptal wall infarction. Angina was alleviated in the five patients who lived. Two of the four patients who died had poor distal runoff demonstrated by arteriography.

Group V: Of this group of 15 patients with three vessel disease and two vessels that could be bypassed, 5 had no alleviation of angina and 2 died. All five patients whose condition did not improve also had poor distal runoff. Of the two who died, one had poor runoff and one died with pump failure associated with acute anteroseptal wall infarction.

Mortality and Prevalence of Myocardial Infarction

Deaths: Twelve of the 100 patients did not survive (Table I). Three patients died in the operating room during prolonged cardiopulmonary bypass. Autopsy in these cases disclosed patency of the saphenous vein bypass grafts, no evidence of acute myocardial infarction, and pulmonary edema due to "pump" failure. Seven other patients died with cardiac failure within 24 hours after operation; autopsy was performed in five of these. Acute anteroseptal myocardial infarction was found in all five; the saphenous vein bypass graft to the left anterior descending artery was patent, but the runoff was poor as demonstrated by arteriography and at necropsy. Another patient died 5 days postoperatively with ventricular fibrillation. At autopsy an acute anteroseptal myocardial infarction was found; the bypass graft to the left anterior descending coronary artery was patent but the distal runoff of this vessel was poor. One patient died 11 days after operation. Autopsy demonstrated a thrombus in the bypass graft

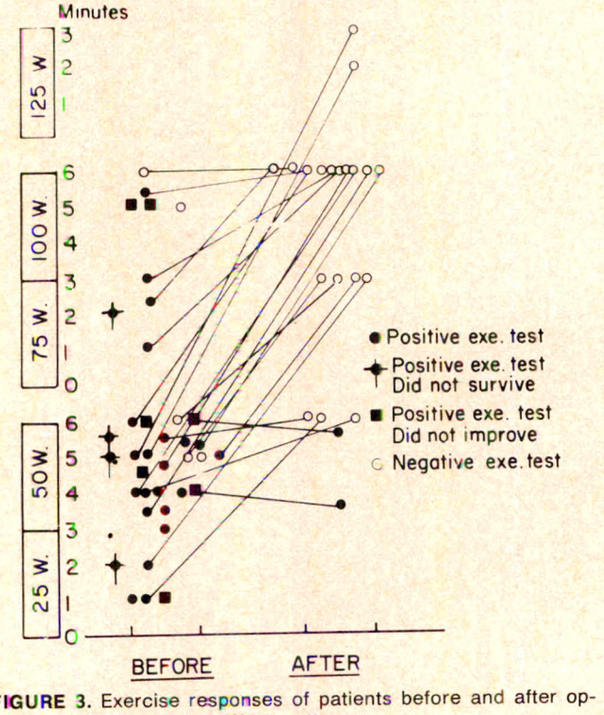

FIGURE 3. Exercise responses of patients before and after operation. exe. = exercise; W. = watts.

to the left anterior descending artery, poor distal runoff of this artery and anterior wall myocardial infarction. Thus, autopsy was performed in 10 of the 12 patients who died, and acute myocardial infarction was the cause of death in 7 of these 10.

Surviving patients: The 88 patients who survived were followed up for 4 to 12 months. Ten patients had electrocardiographic patterns of myocardial infarction within 24 hours after operation; of these 10 patients, 3 manifested clinical improvement and the remaining 7 showed no improvement and persistent angina pectoris. Postoperative coronary arteriography was not performed. The seven patients with persistent angina had poor distal runoff.

Two additional patients had an anteroseptal wall myocardial infarction and clinical deterioration 6 to 12 weeks after operation. The postoperative coronary arteriogram in these patients revealed (1) progression of the proximal obstructive lesions to complete obstruction of the left anterior descending artery; and (2) occluded bypass grafts to this artery. The prevalence rates for postoperative myocardial infarction in the 88 surviving patients were 11 percent for early infarction and 2 percent for delayed infarction (Table I).

Exercise Tolerance

Thirty-seven patients were studied by graded exercise stress tests before operation; 33 had angina pectoris and S–T segment depression of at least 0.5 cm during exercise, and four patients experienced only shortness of breath. Three to 4 months after operation, only 20 patients underwent repeat exercise testing; 18 had a negative response to exercise at a work load similar to or greater than the preoperative work load; 2 had a positive response postoperatively at a level similar to that of the preoperative work load. Seventeen of the 37 patients did not undergo exercise testing after operation: 4 died; 8 with a previous positive exercise study showed improvement after operation but were not available for repeat exercise studies; the remaining 5 patients in this group had recurrent angina pectoris and did not undergo repeat exercise studies (Fig. 3).

Clinical Results in Relation to Flow and Ventricular Function

Ventricular function: Ejection fraction and mean velocity of circumferential fiber shortening per circumference before operation were correlated with the presence or absence of angina pectoris after operation. The ejection fraction of patients whose condition improved ranged from 28 to 75 percent (average 54 ± 11.5 percent [standard deviation]). The ejection fraction of patients who did not show improvement or who died ranged from 10 to 78 percent (average 46 ± 15.5 percent). The difference between ejection fractions in these two groups was significant (P value = 0.05) (Fig. 4). One patient with severe impairment of left ventricular function, as manifested by an ejection fraction of 10 percent, had severe diffuse disease of all three coronary arteries; he did not survive. The mean velocity of circumferential fiber shortening per circumference of patients whose condition improved ranged from 0.37 to 1.47 cm/sec (average 0.89 ± 0.26). The mean velocity of circumferential fiber shortening per circumference of patients who had no improvement or who died ranged from 0.1 to 1.58 cm/sec (average 0.79 ± 0.26). The difference between these two groups was not significant (Fig. 4).

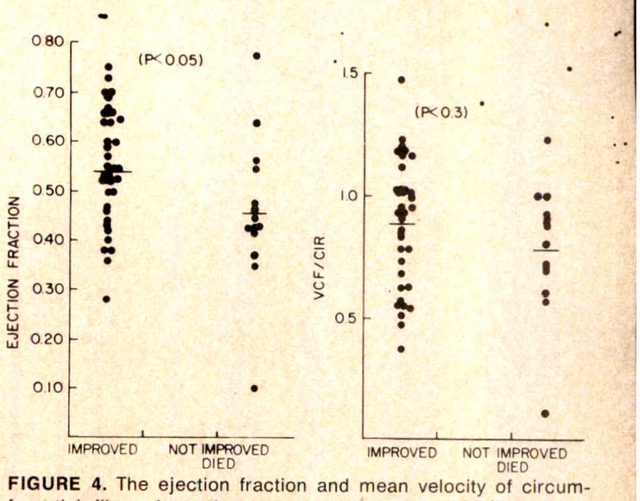

FIGURE 4. The ejection fraction and mean velocity of circumferential fiber shortening per circumference (VCF/CIR) measured in 51 patients preoperatively.

Bypass graft flow: Flow was measured from 86 saphenous vein grafts in 50 patients (Fig. 5). Flow through the bypass to the left anterior descending coronary artery ranged from 20 to 160 cc/min (average 70 ± 38.8 cc) when runoff was good and from 20 to 35 cc/min (average 25 ± 6.1) when runoff was poor. The difference was significant (P value =

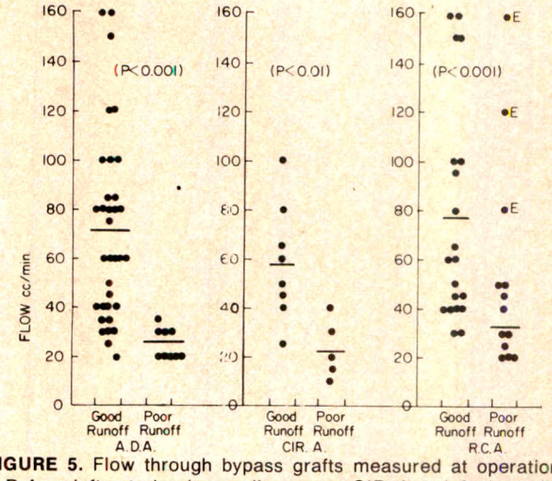

FIGURE 5. Flow through bypass grafts measured at operation. A.D.A. = left anterior descending artery; CIR. A. = left circumflex artery; E = endarterectomy, then bypass graft; R.C.A. = right coronary artery.

0.001). Flow through the bypass graft to the circumflex artery ranged from 25 to 100 cc/min (average 58 ± 23.7) when runoff was good, and from 10 to 40 cc/min (average 23 ± 12) when runoff was poor. This difference was significant (P value = 0.01). Flow through the bypass to the right coronary artery ranged from 30 to 160 cc/min (average of 77 ± 45) when runoff was good, and from 20 to 50 cc/min (average 33 ± 12.3 cc/min) when runoff was poor. This difference was significant (P value = 0.001). In three patients who had poor runoff and who underwent endarterectomy in the distal right coronary artery before bypass grafting, flow was more than 80 cc (Fig. 5). When the coronary arteriogram revealed good distal runoff, flow was greater than 40 cc/min in 79 percent of the bypass grafts to the left anterior descending artery, 75 percent of grafts to the circumflex artery and 70 percent of grafts to the right coronary artery.

Discussion

Clinical Results of Surgery

Relief of angina pectoris: Despite the fairly high surgical mortality rate in our series of patients (12 percent), the clinical results were impressive. Most of the 88 survivors had experienced severe, recurrent angina pectoris before saphenous vein bypass surgery and the operation had been advised because of crippling angina pectoris. After operation, 72 of the surviving patients (82 percent) were completely free of angina pectoris; a great majority have returned to work and are enthusiastic about the relief that they have experienced. Nevertheless, the relief from angina pectoris and the improvement in the quality of life do not constitute proof that the operation is changing the disease process. In many patients vigorous, optimal medical management can accomplish similar results. Regrettably, an untreated control group of similar patients was not available for comparison in terms of long-term survival and their response to medical therapy. The placebo effect must also be considered. Since any surgical procedure unquestionably has a stronger placebo effect than medicine, relief of angina pectoris, although highly desirable, cannot in itself suggest that the disease process has been altered.

The relief of angina pectoris after operation may be due to several important factors. These include (1) reestablishment of adequate blood flow to the ischemic myocardium, (2) possible improvement of left ventricular function, (3) infarction of ischemic areas during and after operation, (4) reduced level of activity, and (5) placebo effect. After operation and during convalescence and rehabilitation, patients are often told to reduce their level of activity.

The operation is designed to improve and reestablish coronary blood flow to ischemic areas. If the shunts are patent and the distal runoff is adequate, then myocardial blood flow should be augmented. In the absence of infarction of ischemic tissue, increased myocardial blood flow should be the primary reason for the impressive relief of angina obtained in this series. Obviously, patency of the graft is necessary for such increased blood flow. Unfortunately, postoperative coronary arteriography was not performed in the symptom-free patients to demonstrate the frequency of graft patency. In the patients who did not show clinical improvement, coronary arteriography after operation demonstrated occlusion of the saphenous vein graft.

Causes of surgical mortality and lack of clinical improvement: Most of the patients who did not survive operation had poor distal runoff demonstrated by coronary arteriography and at necropsy. One patient died because of poor myocardial function, as evidenced by a reduced ejection fraction of 10 percent. Six of the 12 patients who died had myocardial infarction in the anteroseptal area demonstrated at autopsy, resulting in power failure and cardiogenic shock. Although the shunts were patent, distal runoff was poor. Ten other patients experienced myocardial infarction immediately after operation; seven of these showed no clinical improvement and had manifestations of cardiac failure and recurrent angina pectoris.

Sixteen patients continued to have angina pectoris after operation. Poor runoff was noted in 14 of these patients before operation. In only two patients with good runoff, the persistence of angina was attributed to closure of the graft, shown by coronary arteriography. In nine patients with double or triple vessel disease, all the obstructed coronary vessels could not be adequately bypassed because of significant distal atherosclerosis.

Other clinical evidence of improvement: In our experience, the combination of relief of angina pectoris correlated well with improvement in exercise tolerance. The objective findings of left ventricular ischemia on the electrocardiogram were certainly less conspicuous after operation. Again, it is important to emphasize that there were no control subjects. The life cycle of ischemic heart disease is extremely variable, and in a control group properly managed similar improvement in the electrocardiogram may be noted in serial exercise studies. Investigators[10-12] have observed improvement in ventricular function as assessed by exercise hemodynamics, atrial pacing hemodyanmics and cineventriculography after aortocoronary artery bypass grafting.

Patients with overt cardiac failure and large dyskinetic or akinetic areas of the left ventricle were excluded from operation. One patient who had severe hypokinesia of the entire left ventricle with an ejection fraction of 10 percent and a left ventricular end-diastolic pressure of 28 mm Hg did not survive the operation. Seven patients who had severe obstruction of the coronary vessels and a left ventricular end-diastolic pressure of 24 to 30 mm Hg showed postoperative improvement.

Factors Influencing Success of Operation

Graft patency and distal runoff: The success or failure of this operation is determined by the patency

of the graft. Patency ranges from 65 to 90 percent at the end of the first year and, if the grafts are patent then, they generally remain patent for some time thereafter.[14] Many factors influence the patency rate. Perhaps the most important is the size of the distal vessels into which the bypass is directed. The smaller these vessls, the greater the likelihood of occlusion because the flow is reduced. In our experience, patients who did poorly after operation also had poor distal runoff demonstrated by coronary arteriography. Grondin and his associates[15] correlated the patency of aortocoronary artery saphenous vein bypass graft with the amount of flow measured through the bypass at the time of surgery. They found that bypass grafts with a flow greater than 45 cc/min remain patent; bypass grafts that had a flow rate of 20 cc/min or less and that failed to respond to injection of papaverine hydrochloride were closed. They did not correlate the rate of flow with the status of the distal coronary arteries. In our study, there was a striking correlation between the flow measured at the time of surgery and the degree of distal coronary atherosclerosis. It is our impression that distal runoff of these vessels is a major factor in clinical improvement. In our study, only two patients with good distal runoff had a poor result; their angina pectoris was not alleviated. Postoperative coronary arteriograms showed occlusion of the bypass grafts with deterioration of ventricular function, as evidenced by impaired ventricular contraction and reduced ejection fraction. The proximal obstructed lesions in the coronary vessels had progressed to occlusion. Competitive flows are perhaps responsible for the rapid progression of the lesions in the proximal coronary vessels.

The importance of good distal runoff was also evident in the necropsy findings in our patients who died shortly after operation. Five of the seven patients had acute anteroseptal myocardial infarction, with diffuse distal disease of the left anterior descending coronary artery. The bypass grafts were patent in four of these patients who did not survive operation. Death was attributed to complications of postoperative myocardial infarction caused by poor distal runoff. It is our impression that when distal runoff is poor, complications of operative myocardial infarction may ensue and the grafts may eventually close. We therefore believe that the success of the operation is determined by the distal runoff in the presence of adequate ventricular function.

Ventricular function: Values for ejection fraction were compared in patients whose condition improved after operation and those who did not. The left ventricular ejection fraction was significantly higher in the patients whose condition improved, but there was a considerable overlap of data. The ejection fraction reflects the state of myocardial contraction as determined by ventriculography. Most patients with a markedly reduced ejection fraction also had severe distal coronary artery disease. The comparison of mean velocity of circumferential fiber shortening per circumference between these two groups of patients was not statistically significant.

Our studies indicate that the best results of bypass grafting will be obtained in patients with adequate ventricular function and good distal runoff. It is also clear that the operative mortality is greater in patients with impaired ventricular function. Improving blood supply to an area of dyskinesia or akinesia, if it can be accomplished, will be of little or no benefit. Overt cardiac decompensation and conspicuous abnormalities of ventricular function are important factors that increase the risk of operation and the rate of failure. Rea et al.[16] compared the left ventricular function of patients who survived with that of patients who did not survive aortocoronary artery bypass surgery. They found a significant difference in left ventricular function between these two groups: Those who did not survive had greater impairment of ventricular function.

Myocardial infarction: Poor distal runoff may result in no clinical improvement, decreased exercise tolerance, myocardial infarction at operation or progressive shunt closure with myocardial infarction after operation. Myocardial infarction may occur at operation or may be delayed. Delayed myocardial infarction occurs with rapid progression of the original lesion of the coronary artery or closure of the shunt to this artery.

These patients who did poorly after operation generally had poor distal runoff, determined by coronary arteriography or at surgery or necropsy, and their ejection fraction was markedly reduced. Patients who did well with relief of angina pectoris and increased exercise tolerance had good distal runoff and a higher ejection fraction.

It is still not possible to determine whether aortocoronary artery saphenous vein bypass will alter the natural history of coronary artery disease. There are no convincing data that the operation prevents myocardial infarction or alters the mortality rate. Careful randomized studies of patients after coronary arteriography and follow-up for 5, 10 and 15 years may answer this question. A follow-up study of 1 year is reported by Sehapayak and his associates[13]; they found that the mortality at the end of 1 year was similar in the surgically and medically treated groups.

Acknowledgment

We thank Leonard S. Dreifus, MD and William Likoff, MD for their valuable help with this study.

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Closed Chest Model of Intracoronary Occlusion for Study of Regional Cardiac Function

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A new closed chest animal technique permits selective intracoronary balloon occlusion and measurement of hemodynamic and regional metabolic function before and during occlusion and reperfusion. The distal end of the double lumen balloon catheter provides information about the nature and extent of flow distal to the occlusion and permits blood sampling or administration of pharmacologic agents directly into the ischemic zone. Independent blood sampling from the great cardiac vein by means of a specially designed balloon catheter and from the coronary sinus by cannula allows simultaneous biochemical and regional blood flow measurements from the occluded and nonoccluded segments of the heart. Simultaneous intracoronary epicardial electrocardiograms permit electrophysiologic correlation with regional hemodynamic and metabolic events. The administration of oxygen by tracheal airway can increase partial oxygen tension in the circulation distal to coronary occlusion. When intracoronary pressures distal to occlusion are markedly reduced, the frequency of ventricular fibrillation is much greater.

The study of progressive alterations in mechanical and metabolic cardiac function subsequent to coronary occlusion or reperfusion requires complex measurements in an animal model that simulates conditions in man. The development of a reversible model of coronary occlusion could accelerate understanding of the mechanisms of segmental myocardial ischemia, revascularization, cardiac arrhythmias and sudden death, and permit local administration of therapeutic agents into an ischemic segment of the heart. Because a better preparation could provide vital information about the nature of myocardial ischemia, the development of new models for studying mechanisms of coronary occlusion and its life-threatening complications has been given a high priority.[1]

Most assessments of the effects of coronary occlusion on cardiac metabolic and mechanical function are based on measurements that do not distinguish between the contributions of ischemic and nonischemic myocardium, although the two segments respond differently. It is believed a myocardial segment subjected to coronary occlusion will convert to anaerobic metabolism and cease contracting whereas increased demands on the nonoccluded segment may overtax its energy supply, resulting in secondary alteration of mechanical and metabolic function.[2] It has also been postulated that the arteries adjoining the occluded area compensate by increasing flow, and that this increase tends to enhance function of the nonoccluded segment.[3] Therefore, to understand fully the individual effects of occlusion, measurement of function from both ischemic and nonischemic segments must be conducted independently and simultaneously. The

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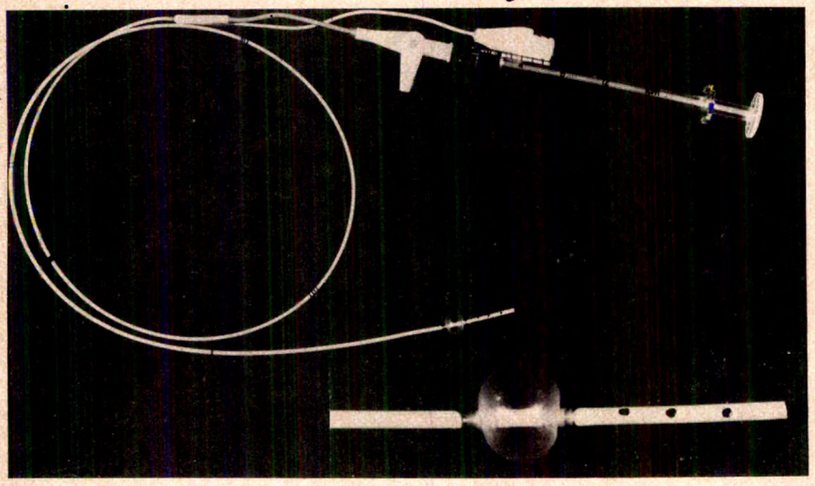

FIGURE 1. Modified double lumen Swan-Ganz balloon catheter. The catheter tip is magnified at **lower right.** The tip protrudes 1 cm beyond the balloon, and its three side holes and end hole are utilized for measuring distal arterial pressure, blood sampling, and inserting intracoronary electrocardiographic electrodes and miniature strain gauges.

new model of experimental coronary occlusion described in this study provides for independent and comprehensive investigations of cardiac function in ischemic and nonischemic myocardium.

Methods

Mongrel dogs weighing 30 to 40 kg were anesthetized with morphine (2 mg/kg intramuscularly) followed 20 to 30 minutes later by pentobarbital (15 mg/kg intravenously). A Harvard respirator provided artificial respiration through a cuffed endotracheal tube. An initial dose of heparin (5 mg/kg) was administered, and further doses of 2 mg/kg were given at 1 hour intervals during the experiment. Supplemental doses of the anesthetic agents were administered whenever necessary to maintain a continuous state of light anesthesia. The amount of fluid lost was estimated and replaced by infusion of physiologic saline solution at a rate of 75 to 100 cc/hour. All the instrumentation and placement of balloon catheters were accomplished in the closed chest preparation.

Instrumentation: A double lumen balloon catheter was adapted for simultaneous occlusion of a coronary artery, sampling of blood and determination of pressure distal to the occlusion. This new intracoronary catheter (Edwards Laboratories, Santa Ana, Calif.), a modification of a Fogarty or Swan-Ganz no. 4F catheter (1.35 mm outer diameter), provides an open lumen extending 15 mm beyond the balloon; the latter can be inflated by air or fluid up to a diameter of 8 mm (Fig. 1). The intracoronary catheter is maneuvered under fluoroscopic control through an angiographic cannula positioned in the left coronary artery. The balloon of the catheter is inflated with Hypaque® sodium 50 percent (weight/volume) (supplied by Winthrop Laboratories) to permit observation of the exact location and control the size of the inflated balloon. This procedure is designed to prevent overdistension of the coronary artery, which may cause epicardial hemorrhage. Occlusion of any specific artery or its branches can be readily achieved by this method. The completeness of occlusion can be demonstrated by coronary angiography[4] and by a sharp reduction in coronary pressure distal to the point of occlusion (Fig. 2). The coronary circulation cut off by the balloon occlusion can be outlined by injection of Hypaque through the central lumen of the intracoronary catheter (Fig. 3). This central lumen is also used to measure retrograde arterial flow, sample blood from the region distal to

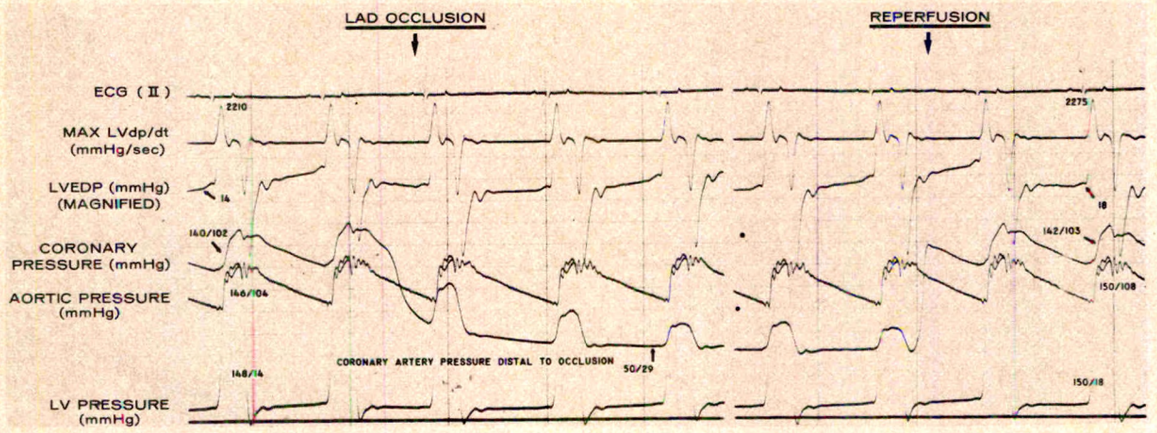

FIGURE 2. Tracings demonstrating that inflation of the intracoronary balloon has occluded the left anterior descending artery. A marked reduction in the distal intracoronary pressure **(arrow)** from 140/102 to 50/29 mm Hg resulted. Deflation of the balloon (REPERFUSION) caused complete restoration of intracoronary pressure. LAD = left anterior descending coronary artery; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MAX = maximal.

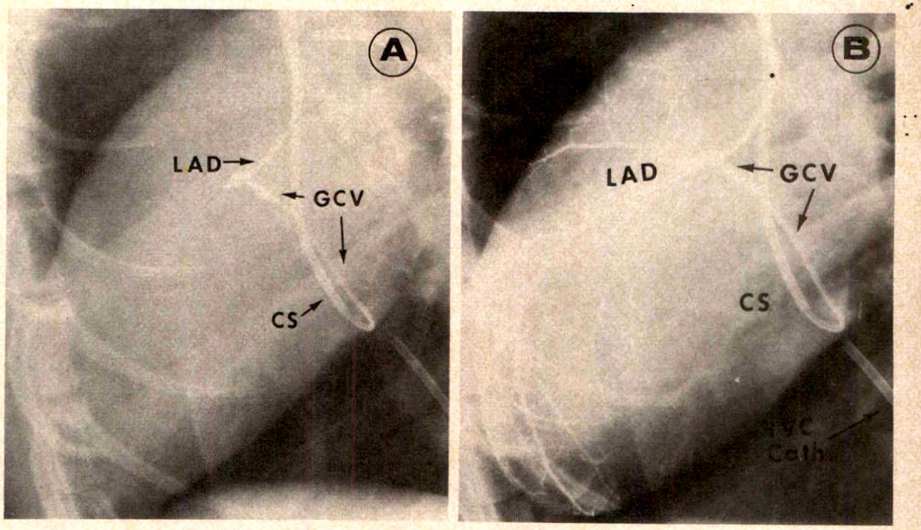

FIGURE 3. Roentgenograms. **A,** demonstrating an intracoronary arterial catheter in the proximal left anterior descending artery (LAD). A great cardiac vein (GCV) catheter has been threaded through the coronary sinus (CS) cannula to approach the balloon occlusion of the left anterior descending artery. **B,** demonstrating distribution of Hypaque® injected into the central lumen of the catheter in the occluded artery to visualize the arterial segment occluded by inflation of the balloon.

the occlusion and assess local mechanical stress and strain. Intracoronary electrocardiograms are recorded by means of a platinum wire protruding through the central lumen of the intracoronary catheter. Reperfusion of the previously occluded area of myocardium can be instituted by gradual or sudden deflation of the balloon (Fig. 2).

A Ganz thermistor catheter is passed into the coronary sinus to obtain blood samples and measure coronary sinus flow by thermodilution.[5] A second double lumen balloon catheter is advanced through a larger guide cannula by way of the coronary sinus until the tip is located deep within the great cardiac vein close to the site of occlusion of the left anterior descending coronary artery (Fig. 3). The central lumen of this catheter is used to collect blood from the great cardiac vein. The balloon near the tip of this catheter is inflated 10 to 15 seconds before sampling. This procedure facilitates separation of blood samples from the coronary sinus and great cardiac vein and allows determination of regional myocardial oxygen consumption as well as lactate, potassium and enzyme balance in both ischemic and nonischemic regions. Thus, simultaneous measurements of regional myocardial blood flow and metabolism may be obtained before and during coronary balloon occlusion, and after reperfusion (Fig. 4).

Hemodynamic and metabolic measurements: Heart rate and cardiac rhythm were determined from the precordial electrocardiogram (lead V_4). A tip transducer catheter (Bio-Tech Instruments, Pasadena, Calif.) was passed from the right femoral artery into the left ventricle to provide measurement of left ventricular pressure and left ventricular end-diastolic pressure. By means of electrical differentiation, the maximal rate of left ventricular pressure rise (dP/dt) was obtained. A Statham P23Db pressure transducer was connected to the central lumen of the intracoronary balloon catheter to measure pressures distal to the point of coronary occlusion (Fig. 2). A similar transducer, connected to a catheter passed through the left femoral artery, was used to measure aortic root pressure and, specifically, peak systolic pressure.

Cardiac output was determined using a Swan-Ganz thermodilution catheter.[6] Stroke work and systemic vascular resistance were computed. Total coronary sinus flow was determined by the Ganz thermodilution technique with the balloon deflated.[5] Regional coronary sinus flow measurements were obtained by temporary inflation of the balloon within the great cardiac vein. Retrograde coronary arterial blood flow could be assessed by direct collection through the central lumen of the intracoronary balloon catheter and this provided samples for measurement of PO_2, lactate and potassium beyond the point of occlusion (Fig. 4).

Control hemodynamic and metabolic data were measured during a 30 minute stable period before occlusion of the left anterior descending or left circumflex coronary artery. Measurements were then performed at 5 minute, 30 minute and hourly intervals after occlusion and, in some instances, after various periods of reperfusion. Simultaneous but separate blood samples were obtained for measurement of lactate and potassium. Lactate was deter-

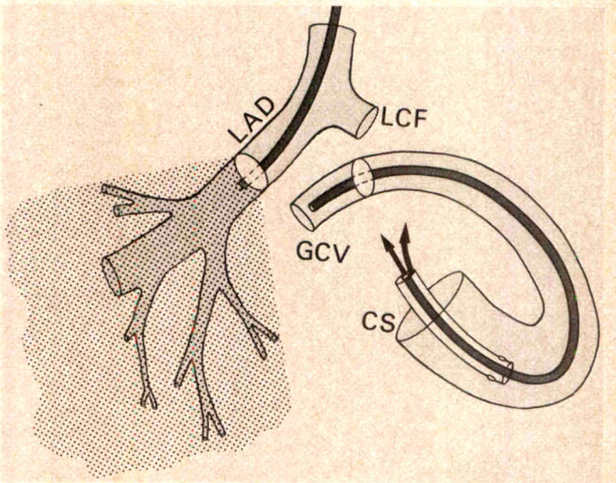

FIGURE 4. Schematic representation of the model of coronary arterial occlusion demonstrating how blood is simultaneously sampled from the great cardiac vein (GCV) draining the occluded and nonoccluded zones perfused by the left circumflex artery (LCF). During collection of blood samples, the balloon in the great cardiac vein catheter is temporarily inflated to separate blood draining the occluded zone from coronary sinus effluent. CS = coronary sinus; LAD = left anterior descending coronary artery.

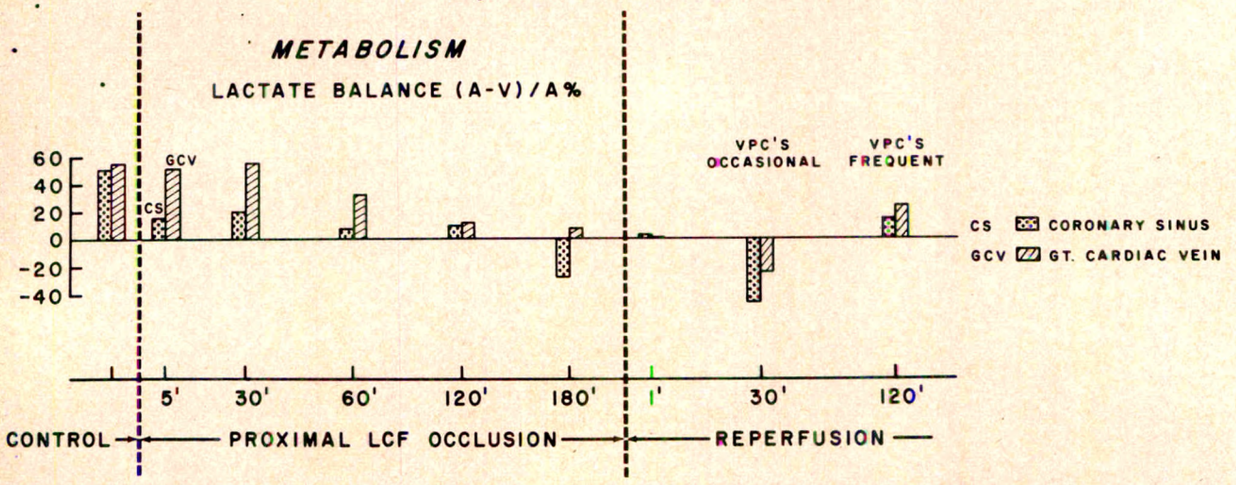

FIGURE 5. Bar graph demonstrating ability of the model to separate venous drainage from the occluded and nonoccluded zones. Lactate measurements were made before and during occlusion of the left circumflex artery and with reperfusion. The coronary sinus blood represents drainage from the occluded zone of the great cardiac vein blood drainage from the nonoccluded segment of the left anterior descending coronary artery. Immediately after occlusion, coronary sinus lactate balance is reduced to 15 percent, indicating abnormal lactate metabolism in the occluded myocardium. After 3 hours of occlusion, the occluded area also shows lactic acid production and the nonoccluded area shows abnormal lactate metabolism. Excellent separation of venous drainage from both segments is evident. Further lactate production occurred during reperfusion (A-V/A) = arteriovenous difference/arterial; VPC's = premature ventricular contractions.

mined by the Hans-Jurgens-Hohorst technique[7] and potassium by means of flame photometry. Both lactate balance and potassium balance were measured from the occluded and nonoccluded regional venous drainage. Blood gases (PO_2 and PCO_2) were monitored throughout the experiment. Hemoglobin and oxygen saturation were measured to provide data for computation of oxygen extraction and regional myocardial oxygen consumption from both occluded and nonoccluded regions. Myocardial arteriovenous creatine phosphokinase (CPK)[8] was measured in several experiments. After the period of occlusion or reperfusion, gross and microscopic examinations were made of the excised heart to assess myocardial damage. Hemodynamic data and intracoronary and standard electrocardiograms were recorded at paper speeds of 50 and 100 mm/sec. The statistical results are expressed as means ± standard error of the mean.

TABLE I

Metabolic Data in 31 Dogs

		Acute LAD Coronary Occlusion	
	Control	30 Minutes	3 Hours
Lactate (%)			
NO [(Ao — CS)/Ao] × 100	34.6 ± 2.2	25.6 ± 2.8	21.1 ± 3.2
O [(Ao — GCV)/Ao] × 100	34.8 ± 2.0	5.6* ± 6.7	10.5* ± 3.7
Potassium (mEq/liter)			
NO (Ao — CS)	−0.05 ± 0.02	−0.13 ± 0.03	−0.13 ± 0.03
O (Ao — GCV)	−0.06 ± 0.02	−0.26* ± 0.05	−0.21* ± 0.04

* $P < 0.05$ relative to nonoccluded segment of the left ventricle.
Ao = aorta; CS = coronary sinus; GCV = great cardiac vein; LAD = left anterior descending coronary artery; NO = nonoccluded segment; O = occluded segment.

Experimental Applications

Selective occlusion of coronary arteries: The desired occlusion of specific arteries or their branches was accomplished without difficulty in 102 animals. The duration of the occlusion extended from several minutes to 8 hours. Ventricular fibrillation occurred in 29 dogs after coronary occlusion, within 30 minutes in 20 dogs and within 3 hours in the other 9. In 14 experiments, at least three coronary arteries were occluded sequentially.

Reperfusion: Reperfusion was performed in 42 dogs through gradual or sudden deflation of the intracoronary balloon after a period of occlusion. Measurements of cardiac function were made for periods of 3 minutes to 5 hours. Regional myocardial metabolic, hemodynamic and coronary flow data are reported for a series of seven dogs during 3 hours of occlusion followed by 5 hours of reperfusion.[9] Stepwise reperfusion was carried out in three dogs by pumping graduated volumes of blood from the left subclavian artery into the central lumen of the intracoronary balloon catheter beyond the occlusion.

Regional measurement of metabolic function: Regional lactate and potassium balances were analyzed from the venous drainage of myocardial segments normally supplied by the occluded and nonoccluded arterial segments (Fig. 5 and 6). Table I indi-

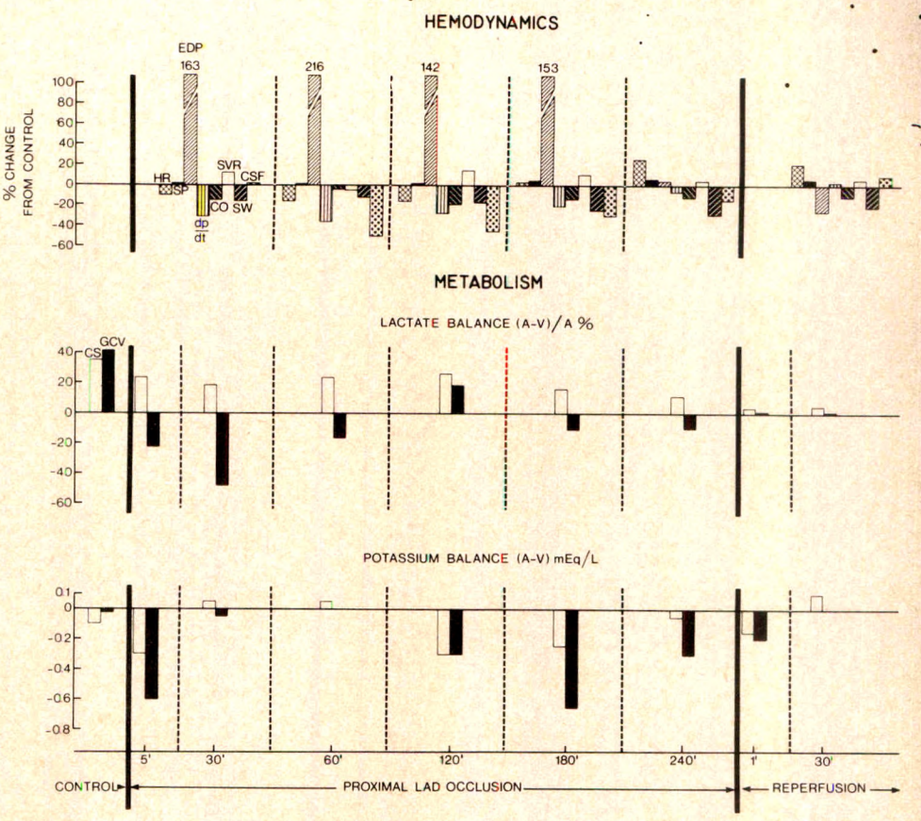

FIGURE 6. Bar graph demonstrating simultaneous hemodynamic measurements and potassium and lactate balance before, during occlusion of the left anterior descending coronary artery, and after reperfusion. Hemodynamic base line represents the control measurements of heart rate (HR) 103 beats/min; systemic pressure (SP) 118 mm Hg; left ventricular end-diastolic pressure (EDP) 10 mm Hg; left ventricular dP/dt 1,348 mm Hg/sec; cardiac output (CO) 2.8 liters/min; systemic vascular resistance (SVR) 3,196 dynes sec cm^{-5}; stroke work (SW) 37 g·m/stroke; and coronary sinus flow (CSF) 97 ml/min. The venous effluent in the great cardiac vein (GCV) represents venous drainage of the occluded zone and in the coronary sinus (CS) drainage of the nonoccluded segment. Note the severe lactate production and potassium loss in the occluded zone (GCV) and also lesser metabolic dysfunction of the nonoccluded (CS) segment. (A-V)/A = arteriovenous difference/arterial.

cates the significant difference between measurements in the two segments and demonstrates the successful separation of metabolic data in a series of 31 dogs. After coronary occlusion, a significant reduction in lactate extraction, often reaching production levels, was observed in the occluded zone. The nonoccluded zone often exhibited abnormal lactate metabolism after coronary occlusion.

Regional coronary flow measurements: The great cardiac vein almost exclusively drains the region of the myocardium perfused by the left anterior descending coronary artery. This great cardiac venous flow enters the coronary sinus and mixes with the venous blood drained from the myocardium perfused by the left circumflex coronary artery. Temporary balloon occlusion of the great cardiac vein provides separation of the venous compartments. Regional coronary blood flow measurements, coupled with arteriovenous oxygen content determinations in the occluded and nonoccluded segments, permit assessment of regional myocardial oxygen consumption.

Coronary venous flow measurements from both the occluded and nonoccluded zones of the myocardium were performed in 16 closed chest dogs during occlusion of the left anterior descending coronary artery. Blood flow measured in the coronary sinus during balloon inflation of the great cardiac vein represented the effluent mainly from the nonoccluded region. Venous drainage of the occluded zone was calculated by subtracting the flow in the nonoccluded region from the coronary sinus flow determined when there was no balloon inflation of the great cardiac vein.

Occlusion of the left circumflex artery was performed in two dogs (Fig. 7). In these animals, coronary sinus flow in the presence of balloon occlusion of the great cardiac vein represented the venous drainage of the occluded region. The flow from the nonoccluded zone was computed by subtracting the flow from the occluded region from the coronary sinus flow measurements made when the great cardiac vein balloon was deflated (Fig. 7, A and B).

Measurements distal to intracoronary occlusion: Coronary arterial pressure distal to intracoronary balloon occlusion was measured in 55 dogs (Fig. 2). Before occlusion, coronary arterial pressure approximated and paralleled that in the aortic root, but upon occlusion it was sharply reduced. Its characteristics then resembled the pressure in the left ventricle.

In one series of 24 dogs, the early coronary peak systolic pressure during occlusion averaged 43 mm Hg (a decrease of about 70 percent from the control level). The diastolic phase of coronary arterial pressure remained about the same during the 4 hours of occlusion.

In 9 of the 24 dogs ventricular fibrillation developed within the first hour after occlusion and defibrillation attempts were not successful. The mean postocclusion coronary arterial diastolic pressure in

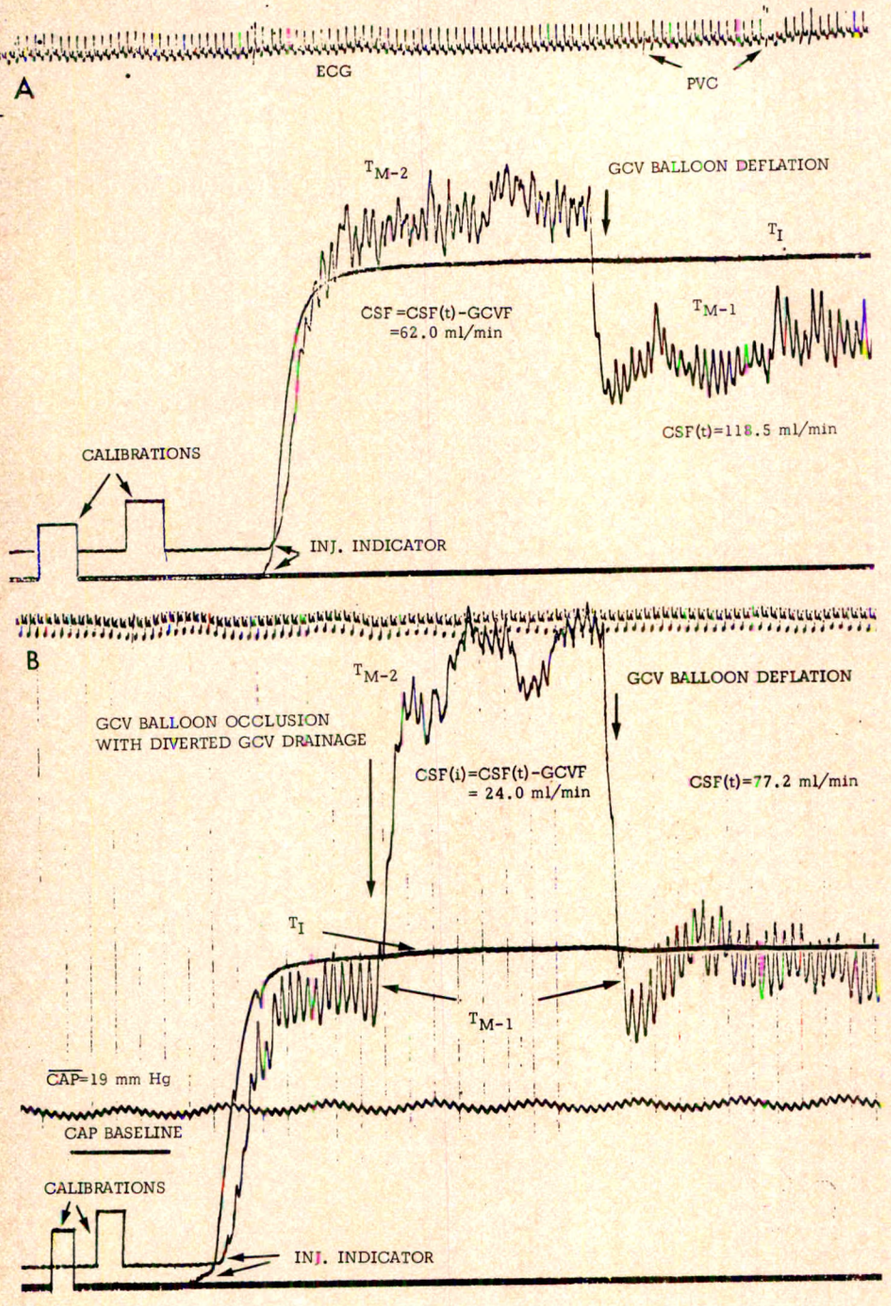

FIGURE 7. Regional coronary flow measurements by thermodilution technique. **A,** before occlusion of the left circumflex coronary artery. With the great cardiac vein (GCV) balloon inflated, the regional coronary sinus flow (total coronary sinus flow minus great cardiac vein flow) measures 62.0 ml/min. With the balloon deflated, total coronary sinus flow is 118.5 ml/min. **B,** during occlusion of the left circumflex artery, with the cardiac vein balloon inflated, the coronary sinus flow which represents the occluded area is decreased to 24 ml/min. When the balloon is deflated, the total coronary sinus flow is 77.2 ml/min. $\overline{CAP}$ = mean coronary arterial pressure.

these dogs was 12.0 ± 1.2 mm Hg. The remaining 15 dogs had no ventricular fibrillation after occlusion and had a higher level of mean diastolic coronary arterial pressure (19.1 ± 1.6 mm Hg). The statistical difference between these two groups was significant ($P > 0.02$).

Retrograde arterial blood flow through the central lumen of the intracoronary catheter beyond the point of occlusion demonstrated a high level of oxygen saturation, paralleling that of the aortic blood. Blood samples from this region were compared during breathing of room air and oxygen (Table II). The results indicate that administration of oxygen can increase PO_2 in the collateral circulation distal to the coronary occlusion.

Intracoronary epicardial electrocardiogram: In 11 closed chest dogs the intracoronary epicardial electrocardiogram was monitored during the coronary occlusion simultaneously with a precordial electrocardiogram. Figure 8 shows the comparison of an epicardial lead with a tracing of lead V_4 obtained during occlusion of the left anterior descending coronary artery in a dog that underwent shock 2 hours after occlusion. The epicardial electrocardiogram re-

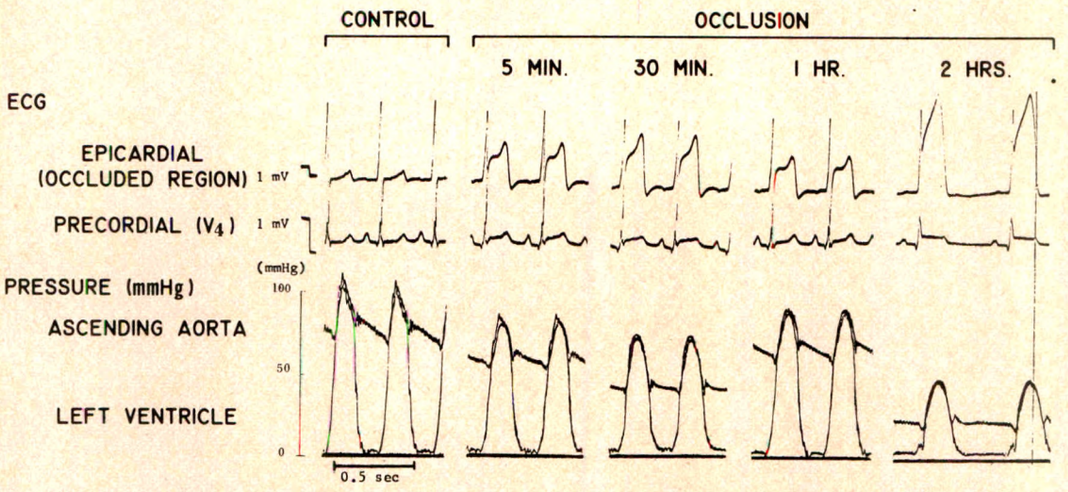

FIGURE 8. The epicardial intracoronary electrocardiogram in closed chest dog recorded in the occluded zone demonstrates marked S–T segment elevation after balloon occlusion which becomes more pronounced with progressive reductions in systemic pressure. A precordial V_4 tracing with much greater standardization is simultaneously recorded to demonstrate the greater voltages obtained by the intracoronary electrocardiogram.

vealed much greater voltages and a more pronounced current of injury than the conventional V_4 lead. When severe hypotension occurred, the S–T segment elevation of the intracoronary epicardial lead correlated inversely with left ventricular systolic pressure measurements.

Residual potassium measurements of ischemic and nonischemic myocardium: Myocardial tissue samples were obtained at the end of the experiment from the ischemic and nonischemic regions and the borderline intermediate zones of the left ventricle for measurement of their potassium content. These data may be important in checking the veracity of myocardial potassium balances in the beating heart and in assessing the extent of regional myocardial damage and the effectiveness of therapeutic agents.[9]

Arteriovenous differences in enzyme CPK: After occlusion of the left anterior descending coronary artery, arteriovenous differences in CPK were determined from the great cardiac vein and aorta. No significant increase in CPK from either area was noted in the first 3 hours, but after 4 hours, a distinct change in the arteriovenous differences was observed.

Selective infusions into the ischemic zone: Blood flow from the left subclavian artery was channeled by connecting a catheter externally into a distal segment of the occluded artery so that the ischemic area could be reperfused at various flow rates to determine effects of flow rate on myocardial func-

TABLE II

Effect of Oxygen Administration on Coronary Arterial PO_2 in 15 Dogs

		Left Anterior Descending Occlusion		
	Control	1st Hour Room Air	2nd Hour 100% O_2 Administration	3rd Hour Room Air
Aortic PO_2	100 ± 14.3	100.6 ± 15.5	396.0 ± 40.8	85.4 ± 6.0
Coronary arterial PO_2*	99 ± 13.8	90.5 ± 11.0	322.0 ± 30.3	80.2 ± 5.8
P value	NS	NS	NS	NS

* Distal to occlusion of the left anterior descending artery.
NS = nonsignificant.

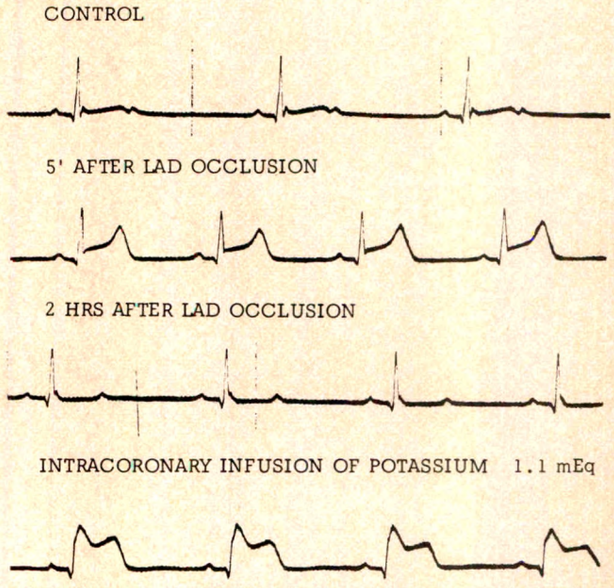

FIGURE 9. Effect on the electrocardiogram (lead V_4) of infusing 1.1 mEq potassium into the ischemic zone through the central lumen of the catheter in the left anterior descending coronary artery.

tion. Various pharmaceutical agents, such as potassium (Fig. 9) and alleged vasodilators, were also infused through the central lumen of the intracoronary catheter into the region beyond the balloon occlusion to determine their effect on the peripheral coronary bed and regional metabolism.

Measurement of cardiac function during arrhythmias: After an initial 5 minutes of occlusion of the left anterior descending coronary artery, 3 of 17 dogs had ventricular tachycardia; 14 continued to have normal sinus rhythm. Myocardial potassium balances from nonischemic and ischemic areas were compared during sinus rhythm and ventricular tachycardia (Fig. 10). During sinus rhythm, potassium concentration from the occluded zone of the great cardiac vein increased significantly to 8 percent above the control level before occlusion, but remained relatively constant in the nonoccluded segment. When ventricular tachycardia occurred, the net myocardial potassium loss increased in both the occluded and nonoccluded segments of the heart to 13 percent above the preocclusion level, thereby suggesting that the nonoccluded myocardium may also be seriously affected by arrhythmias.[10]

Discussion

A recently published report of a task force of the National Heart and Lung Institute[1] concluded: "There is no adequate animal model for simulating human coronary heart disease. Consequently, much of the indicated investigation must be carried out in man until such time as an adequate model becomes available. The importance of a good animal model for clinical coronary heart disease exhibiting myocardial infarction, arrhythmia, and sudden death were repeatedly emphasized. If such were available, studies of blood flow, collateral circulation development, drug action, and the effects of surgical revascularization could be subjected to critical evaluation prior to their application in man. The development of such an animal model can accelerate progress in many areas and must, therefore, be given high priority." The panel recommended the development of animal models that would permit (1) quantitation of myocardial ischemia for use in trials of medical and surgical therapy, (2) study of the metabolic, mechanical and electrophysiologic properties of the ischemic myocardium with special attention to the pathogenesis of arrhythmias and the protection of the ischemic myocardium, and (3) study of the relations of arrhythmias and sudden death due to coronary artery disease, to expedite and accelerate progress in the development and testing of preventive and therapeutic agents, devices and surgical procedures.

In spite of certain objections, the dog preparation has been widely used in gathering data essential to the study of mechanisms of myocardial disease.[11] Obviously, the physiologic differences between man and the dog may affect the interpretation and application of experimental data in the clinical setting. Nevertheless, since the dog is sufficiently similar to man physiologically and metabolically and since the limitations of extensive experimentation in man are so prohibitive, application of data obtained from the dog can be justified. Anesthesia, invasive measurements, catheterization and other interventions also may introduce significant artifacts. Sham experiments performed in the same fashion as the experimental series act as a control and rule out possible artifacts. Investigations of the effects of coronary occlusion should encompass simple models that can be used for study of acute occlusion of a single artery or chronic multiple occlusion configurations. The model described here provides a valid physiologic simulation for the study of regional as well as global cardiac function, to compare preocclusion control data with the alterations that occur after occlusion and subsequent reperfusion or other interventions.

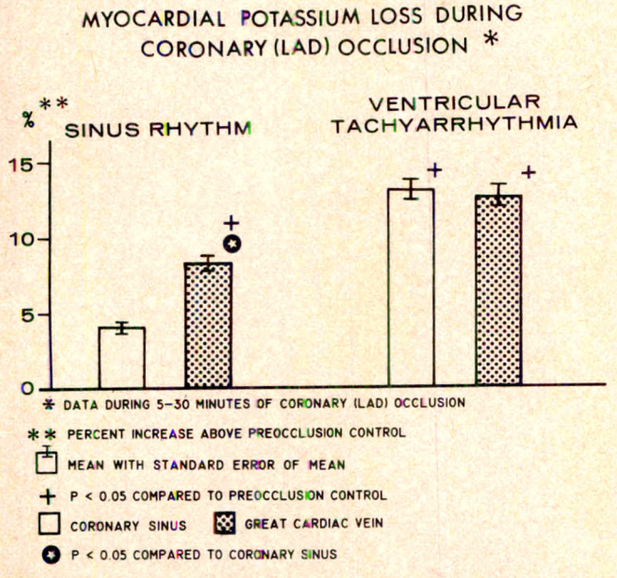

FIGURE 10. Statistical comparison of myocardial potassium loss after occlusion of the left anterior descending artery (LAD) during sinus rhythm and ventricular tachycardia. **White bars** represent percent change from control potassium levels in coronary sinus blood and **stippled bars,** that of the great cardiac vein. Occlusion of the left anterior descending artery caused a more significant rise in potassium in the great cardiac vein. During ventricular tachycardia, both coronary sinus and great cardiac vein effluent exhibit a significant increase in potassium concentration relative to preocclusion control levels.

Evaluation of Other Models for Studying Coronary Occlusion

Information derived from open chest animal experiments must be viewed with caution because changes in intrathoracic pressure and in the temperature of the myocardium can affect cardiac output and reduce it as much as 50 percent.[12] Hence, there has been increasing emphasis on closed chest models of occlusion. These include "shot-gun" microsphere embolization of the coronary arteries[13] or selective embolization of one or two of their major branches.[14,15] A modification consists of embolization by

means of mercury.[16] Embolized particles may be found in either pulmonary or systemic peripheral vessels, causing false alterations in peripheral vascular resistance and afterload. Mercury may have toxic effects on the myocardium and other organs. The presence of solid particles within the myocardial zone of coronary occlusion could modify regional compliance and contraction and seriously alter functional measurements. Diffuse obstruction of the coronary microvasculature by beads or mercury may lead to excessive depression of cardiac function, which does not simulate human coronary occlusion.

Local coronary arterial thrombosis has been produced by electrical cauterization or use of an intracoronary spiral wire,[17,18] but it is difficult to assess the actual time course and development of the intravascular thrombosis. Such electrical and mechanical stimulation and thermal effects may cause unusual myocardial damage, resulting in disruption of the depolarization-repolarization cycle, electrical instability and associated hemodynamic and metabolic derangements. Recently, investigators have also utilized insertion into a coronary artery of a solid or hollow cylinder,[19-21] spiral wire,[22,23] plastic cones,[24] steel balls[25] or lead foil.[26] Such methods permit study of acute and gradual occlusion; however, because the occluders migrate, they do not provide control of location of the occlusion. In addition, these techniques may be accompanied by significant artifacts, and do not insure completeness of occlusion.[19] These modes of coronary occlusion are not reversible, but the use of circulating magnetic products has recently been reported[27] to provide a controlled occlusion technique that is also irreversible.

Many investigators are using long-term implantation of hydraulic or pneumatic cuffs[28,29] or ameroid constrictors[30,31] around selected coronary arteries to provide coronary occlusion. These procedures require previous thoracotomy and pericardiotomy, which may result in adhesions, fibrosis, interruption of coronary innervation[32] and interference with coronary veins, all of which may alter cardiac function. Therefore, a well controlled, flexible and totally reversible mode of coronary balloon occlusion was devised to simulate the human occlusion and to offer a more complete technique for the study of cardiac metabolic, hemodynamic and mechanical function, both regional and global.

Capabilities of Occlusion-Reperfusion Model

To date, the new closed chest model has been successfully applied in 102 dogs to perform the following procedures:

1. Selective intracoronary balloon occlusion of specific coronary arteries and their branches. The occlusion can be complete or partial and sudden or gradual.
2. Sequential occlusion of the left anterior descending, left circumflex or right coronary artery, or any combination of the main arteries or branches.
3. Reperfusion (sudden or gradual) by deflation of the occluding intracoronary balloon.
4. Regional metabolic measurements of pH, myocardial oxygen consumption, lactates, electrolytes, enzymes and fatty acids from occluded and nonoccluded segments.
5. Determination of regional coronary flow from ischemic and nonischemic myocardium.
6. Stress-strain measurements of regional myocardium.
7. Intracoronary electrocardiogram of the ischemic and nonischemic zones.
8. Local infusion of pharmaceutical agents through the central lumen of the intracoronary balloon catheter.
9. Residual tissue measurements of myocardial enzymes and electrolytes.
10. Correlation of hemodynamic and metabolic data with pathologic findings.

The completeness of the balloon occlusion was demonstrated by coronary angiography[4] and also by pressure tracings, which revealed typical alterations in pressure distal to the occlusion (Fig. 2). It was essential to determine whether positioning of the uninflated balloon catheters within the coronary arteries might interfere with flow in the regional myocardium subserved by that coronary artery. Specifically designed experiments utilizing electromagnetic flowmeters revealed that deflated no. 4F catheters did not affect the rates of coronary blood flow.

Applications

The new closed chest occlusion-reperfusion model provides a means of studying simultaneous but separate measurements of regional metabolic function in the occluded and nonoccluded zones of the heart. The coronary sinus receives 70 to 95 percent of the total venous drainage from regions of the heart perfused by the left anterior descending and circumflex arteries.[33] The great cardiac vein drains the region perfused by the left anterior descending artery and empties into the coronary sinus. Thus, coronary sinus blood normally represents a mixture of both venous drainages. After temporary balloon occlusion of the great cardiac vein, blood in the coronary sinus represents venous drainage from the region perfused by the left circumflex artery. Anatomic studies have occasionally shown the existence of veno-venous shunts between the great cardiac vein and the coronary sinus.[34] Our angiographic studies confirm the presence of small shunts; their exact volume is now being determined by isotope studies.[34] Total separation of venous drainage may not be physiologically feasible, because an overlap of coronary arterioles from adjoining vessels or those branching off above the site of occlusion may dilute measurements of metabolic function from the ischemic zone. One of the main conclusions from numerous measurements performed to date is that the regional metabolic data from the occluded site differ significantly from those based on coronary sinus samples (mixed venous drainage from areas perfused by the left anterior descending and left circumflex arteries). Therefore, the metabolic consequences of an occlusion of the left

anterior descending coronary artery are best studied by direct measurements of venous drainage directly from the zone of ischemia rather than by inferring, as in the past, that coronary sinus blood samples demonstrate alterations in metabolic function of a localized zone of ischemia.

When the left circumflex artery is occluded, drainage from the great cardiac vein represents the venous return from the nonischemic zone perfused by the left anterior descending artery. Venous drainage from the ischemic myocardium is represented by the coronary sinus effluent when the great cardiac vein balloon is inflated. This coronary sinus effluent may be slightly contaminated by drainage from the right coronary artery.

Measurement of regional flows by our technique, which separates the venous blood draining occluded and nonoccluded segments, allows assessment of regional myocardial oxygen consumption and quantification of myocardial lactate and potassium balances. Correlation of these metabolic measurements with segmental coronary flow and regional myocardial hemodynamics in the closed chest provides information required for the better understanding of ischemic mechanisms.

Comparison of the intracoronary epicardial electrocardiogram with the precordial electrocardiogram demonstrated that the former provided greater amplitude and much more detail for the study of S–T segment elevation. The electrocardiographic alteration correlated closely with the physiologic state reflected by either systemic or coronary perfusion pressures. One important feature of the new model is its provision of a simple method of reversing coronary occlusion for study of reperfusion mechanisms and their effects on myocardial viability.[9] Additionally, the intracoronary balloon catheter has a central lumen that allows communication with the region distal to the balloon occlusion. This capability has been utilized for the following:

1. Indirect assessment of coronary collateral vessels by study of alterations in retrograde blood, coronary flow and pressure distal to the occlusion.
2. Blood sampling from the ischemic myocardium beyond the inflated balloon.
3. Provision at a regional intracoronary electrocardiogram by insertion of a platinum wire through the lumen into the occluded zone.
4. Drug infusions through the central lumen, thus permitting selective pharmacologic interventions whose effects in the ischemic region can be isolated from systemic effects. Among present studies to be reported are controlled rates of infusion of saline solution, arterial and venous blood into the occluded region to compare the effects of anoxia, hypoxia and ischemia, evaluation of alleged vasodilator drugs and other factors affecting coronary collateral circulation.
5. Assessment of regional myocardial mechanical function. We have devised miniaturized force and stress gauges that may be inserted in the closed chest preparation by means of the intracoronary catheter and wedged within a branch distal to the occlusion.[35] The localization and insertion of miniature gauges into the endocardium through a left ventricular catheter is also being investigated.[36] The ability to quantitate regional mechanical forces in this manner is being critically evaluated.

Clinical application of regional metabolic measurements is currently being studied at this center. Blood samples collected from a catheter in the coronary sinus and a second catheter advanced into the great cardiac vein allow regional sampling. Preliminary data confirm the value of performing regional and global metabolic determinations.

Acknowledgment

We thank Olga Diner, Jules Osher, Willis Curtis Pea, Myles Prevost, John Friedman, Steven Roven, Jeanne Bloom and Elaine Calmenson for their technical assistance. We also appreciate the assistance of Dr. Glenn Langer as consultant on this study.

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Progressive Alterations of Cardiac Hemodynamic and Regional Metabolic Function After Acute Coronary Occlusion

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Hemodynamic and regional metabolic function was assessed simultaneously in 34 closed chest dogs during a preocclusion control period and 3 hours of intracoronary balloon occlusion of the proximal left anterior descending artery. The data indicate immediate alteration in hemodynamic measurements with many fluctuations in the 3 hour occlusion period. No specific hemodynamic pattern was evident. When the mean data were analyzed, occlusion was found to cause early increases in left ventricular end-diastolic pressure (43 percent) and systemic vascular resistance (21 percent), and decreases in peak systolic pressure (5 percent), maximal rate of rise of left ventricular pressure (dP/dt) (20 percent), cardiac output (19 percent), stroke work (26 percent) and coronary sinus blood flow (19 percent).

Regional metabolic measurements showed significantly different metabolic function in the occluded and nonoccluded zones of the left ventricle. Lactate balance decreased to near production levels, and a substantial potassium loss occurred in the occluded zone shortly after occlusion; lactate and potassium balances later fluctuated, but usually remained depressed. Abnormal lactate metabolism and potassium efflux were often observed in the nonoccluded zone. A 6 to 8 percent increase in oxygen extraction was noted in both segments.

Progressive alterations in hemodynamic and metabolic function of the heart after coronary occlusion are not uniform and exhibit dynamic fluctuations. Although a direct relation was noted between the degree of metabolic dysfunction and hemodynamic change, individual experiments often revealed a distinct metabolic-mechanical dissociation.

The progressive consequences of myocardial ischemia are difficult to study in man since preocclusion control data are rarely available, and complex invasive regional measurements cannot readily be performed. Hence, much of the needed basic information must be derived from animal experimentation. Many animal models of coronary occlusion have been used, but most of them are deficient because they (1) involve open chest preparations that greatly alter cardiac function, (2) do not properly simulate coronary occlusion in man, or (3) do not permit simultaneous and separate metabolic evaluation of the occluded and nonoccluded zones of the myocardium.[1]

In the preceding report[1] we described a new closed chest model for production of localized intracoronary occlusions of coronary arteries. This model features simultaneous determinations of hemodynamic status and regional metabolic function, myocardial flow and oxygen consumption. The purpose of this study is to provide information about the progressive response of the intact heart preparation to coronary occlusion and to supply data that might be used as a base line for subsequent evaluations of the effects of reperfusion, pharmaco-

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TABLE I

Hemodynamic and Metabolic Data in 34 Dogs (means ± standard error of the mean)

	Control	Time after LAD Occlusion				
		5 Minutes	30 Minutes	1 Hour	2 Hours	3 Hours
Heart rate (beats/min)	109 ± 5.6	115 ± 6.0	117 ± 7.0	115 ± 8.0	121 ± 7.0	128* ± 7.0
Peak systolic pressure (mm Hg)	141 ± 3.0	134* ± 3.0	135* ± 3.0	135* ± 3.0	136* ± 3.0	133* ± 3.0
LV end-diastolic pressure (mm Hg)	7 ± 0.6	10* ± 0.8	10* ± 0.8	11* ± 0.9	11* ± 0.8	11* ± 0.9
LV dP/dt (mm Hg/sec)	2842 ± 135	2273* ± 124	2278* ± 112	2217* ± 109	2268* ± 125	2311* ± 125
Cardiac output (liters/min)	2.70 ± 0.18	...	2.18* ± 0.12	2.12* ± 0.13	2.21* ± 0.14	2.30* ± 0.15
Systemic vascular resistance (dynes sec cm^{-5})	3743 ± 242	...	4522* ± 282	4791* ± 331	4523* ± 283	4267 ± 295
Stroke work (g-m/beat)	42 ± 3.0	...	31* ± 2.5	32* ± 2.6	32* ± 2.7	29* ± 2.5
Coronary sinus flow (ml/min)‡	125 ± 13	...	101 ± 12	110 ± 13	109 ± 12	108 ± 12
Lactate balance (%)						
Nonoccluded (Ao-CS)/Ao × 100	34.4 ± 2.0	23.5* ± 2.9	26.2* ± 3.0	25.8* ± 2.4	19.8* ± 3.4	23.7* ± 3.1
Occluded (Ao-GCV)/Ao × 100	35.0 ± 1.8	6.1*† ± 6.8	−1.0*† ± 6.7	10.8*† ± 4.8	7.3*† ± 4.6	7.8*† ± 4.0
Potassium balance (mEq/liter)						
Nonoccluded (Ao-CS)	−0.04 ± 0.02	−0.21* ± 0.04	−0.13* ± 0.03	−0.06 ± 0.04	−0.17* ± 0.03	−0.13* ± 0.03
Occluded (Ao-GCV)	−0.06 ± 0.02	−0.35*† ± 0.05	−0.26*† ± 0.05	−0.21*† ± 0.07	−0.25*† ± 0.03	−0.22* ± 0.04
Oxygen saturation (%)						
Nonoccluded (Ao-CS)	56.9 ± 1.6	62.5* ± 1.5	62.3* ± 1.5	62.9* ± 1.5	63.7* ± 1.7	64.0* ± 1.4
Occluded (Ao-GCV)	56.6 ± 1.6	62.8* ± 1.3	63.8* ± 1.2	64.7* ± 1.4	64.9* ± 1.5	64.9* ± 1.3

* $P < 0.05$ relative to preocclusion control level.
† $P < 0.05$ relative to nonoccluded segment of the left ventricle.
‡ no. = 15 dogs.
Ao = aorta; CS = coronary sinus; GCV = great cardiac vein; LAD = left anterior descending coronary artery; LV = left ventricular.

logic treatment, circulatory assistance or other interventions.

Methods

The methods used for induction of anesthesia and maintenance of body fluids in closed chest dogs are reported in the preceding article.[1] The application of intracoronary balloon catheters for occluding specific coronary arteries and for simultaneous measurements of hemodynamics, myocardial blood flow and metabolic functions of occluded and nonoccluded myocardial segments are also previously described and for brevity referred to hereafter as the Corday-Lang model.[1]

The proximal left anterior descending coronary artery was selected for a 3 hour acute occlusion by means of an intracoronary balloon catheter. Venous drainages from the myocardium supplied by the occluded left anterior descending coronary artery and from the nonoccluded region were separated during sampling by the temporary inflation of a balloon at the tip of a catheter positioned within the great cardiac vein. This procedure permits determination of regional lactate and potassium arteriovenous balances, coronary flow rates and myocardial oxygen consumption. Pressure measurement and sampling beyond the point of occlusion were performed by way of the central lumen of the intracoronary balloon catheter.

Duplicate hemodynamic and metabolic measurements were carried out during a 30 minute stabilization, preocclusion control period. After inflation of the intracoronary balloon, measurements were performed 5 and 30 minutes and 1, 2 and 3 hours after occlusion.

To provide sham base-line data and to assess the effects of anesthesia as well as other procedures in the preparation used, five fully catheterized and fully instrumented dogs were studied without coronary arterial balloon inflation over a period of time equivalent to that of the occlusion study. Hemodynamic measurements were recorded and blood was collected for metabolic determination at exactly the same time intervals as those provided in the occlusion protocol. The excised hearts were examined to assess myocardial damage.

All data were subjected to statistical analysis by computing mean and standard error of mean values. Paired t tests for significance comparisons were carried out relative to preocclusion control data, and between measurements performed simultaneously in the occluded and nonoccluded arterial segments of the left ventricle. Data from individual experiments were studied in addition to the statistical mean trends.

Results

The proximal left anterior descending coronary artery was acutely occluded in closed chest dogs for 3 hours. Thirty-nine animals survived the 3 hour occlusion during which experimental observations were conducted. Five of the 39 dogs were excluded from

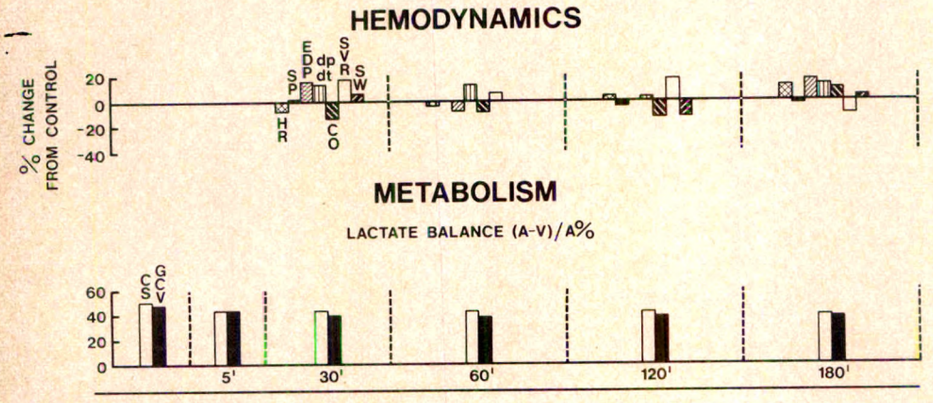

FIGURE 1. Hemodynamic and metabolic measurements recorded over a 3 hour period in the sham series of 5 dogs, prepared with instrumentation similar to that for the study series of 34 dogs. Coronary arteries were not occluded. Bar graph demonstrates hemodynamic changes from base-line control values, expressed as percent change from control. Control measurements were: Heart rate (HR) 79 beats/min; aortic systolic pressure (SP) 168 mm Hg; left ventricular end-diastolic pressure (EDP) 12 mm Hg; left ventricular dP/dt (dp/dt) 1,417 mm Hg/sec; cardiac output (CO) 2.2 liters/min; systemic vascular resistance (SVR) 5,284 dynes sec cm^{-5}; and stroke work (SW) 50 g·m/beat. The lower line demonstrates lactate balance. Although there is some mild fluctuation, there is no significant difference between the zones perfused by the left anterior descending (great cardiac vein [GCV] samples), and left circumflex (coronary sinus [CS] sampling with temporary GCV occlusion) arteries. (A-V)/A = arteriovenous difference/arterial.

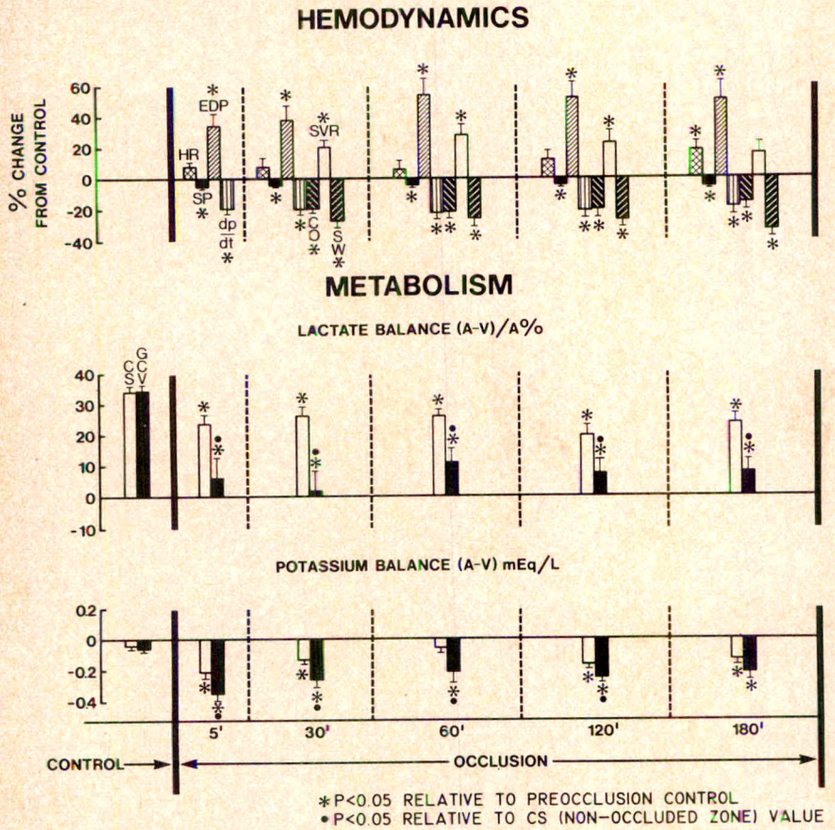

FIGURE 2. Mean measurements of hemodynamic and metabolic function made in 34 dogs during a control period and after 3 hours of coronary occlusion. The top bar graph demonstrates hemodynamic percent changes from base-line control levels. Control measurements were heart rate 109 beats/min; systolic pressure 141 mm Hg; left ventricular end-diastolic pressure 7 mm Hg; left ventricular dP/dt, 2,842 mm Hg/sec; cardiac output 2.8 liters/min; systemic vascular resistance 3,680 dynes sec cm^{-5}; and stroke work 43 g-m/beat. Thirty minutes after occlusion there was a significant decrease in maximal left ventricular dP/dt, cardiac output and stroke work and an increase in systemic vascular resistance which persisted over a 3 hour period. The occluded zone (great cardiac vein) demonstrated abnormal lactate metabolism throughout the entire 3 hour occlusion. Potassium balance showed an intermittent loss from the nonoccluded (coronary sinus) zone and persistent loss from the occluded zone for the 3 hour period. Abbreviations as in Figure 1.

this study because they underwent severe hypotension and fulfilled the criteria adopted for designating cardiogenic shock (30 percent or greater reduction in both cardiac output and systolic pressure). These animals are the subject of a subsequent report on factors that apparently precede the onset of the shock state.[2] This study of the remaining 34 dogs (Table I) is concerned with progressive events in animals that remained normotensive after acute occlusion of the proximal left anterior descending coronary artery.

Series A—Hemodynamic and Metabolic Measurements in Sham Preparation

Five dogs were prepared with instrumentation and placement of catheters identical to those of the 34

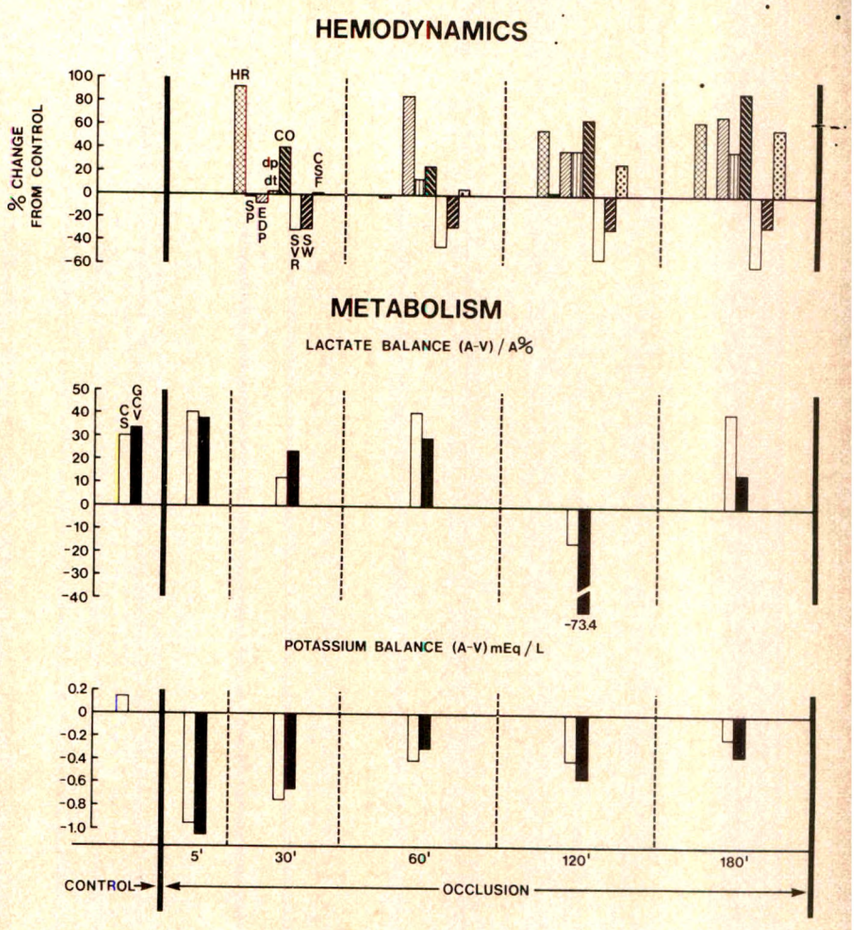

FIGURE 3. Hemodynamic and metabolic measurements made during a control period and 3 hours of coronary occlusion in a dog. Hemodynamic function is reported as percent change from base-line control levels. Control measurements were heart rate 84 beats/min; systolic pressure 162 mm Hg; left ventricular end-diastolic pressure 13 mm Hg; left ventricular dP/dt 2,455 mm Hg/sec; cardiac output 1.5 liters/min; systemic vascular resistance 6,611 dynes sec cm^{-5}; stroke work 30.5 g-m/beat; and coronary sinus flow 90 ml/min. Abnormal lactate metabolism occurred in the nonoccluded (coronary sinus) segment 30 minutes after balloon inflation; lactate production occurred 2 hours after occlusion in both zones. There was a consistent potassium loss in both the occluded and nonoccluded segments during the 3 hours of occlusion. Abbreviations as in Figure 1.

dogs in the occlusion series, but the coronary arteries were not occluded. Figure 1 illustrates hemodynamic and regional metabolic measurements in a typical sham dog. During 3 hours of observation, all five dogs demonstrated a rising heart rate (from 105 to 132 beats/min), fluctuations in cardiac output and systemic vascular resistance and a minor decrease in peak systolic pressure (from 150 to 146 mm Hg). These effects may be due to the influence of initial and supplemental anesthesia. Regional lactate extraction and myocardial potassium balances showed mild fluctuations, but there was no significant difference in metabolic measurements in zones perfused by the left anterior descending and left circumflex coronary arteries.

Series B—Hemodynamic and Regional Metabolic Measurements During 3 Hours of Coronary Occlusion

I. Hemodynamics

Heart rate: During the 3 hour occlusion period, the mean heart rate rose progressively from 109 to 128 beats/min (Table I, Fig. 2 to 4). This 18 percent increase is comparable to that noted in the five sham dogs in Series A that did not undergo occlusion. Nineteen of these 34 dogs had an increased heart rate during occlusion; the rate decreased in 8 dogs, and remained relatively unchanged in 7. Transient arrhythmias produced by ischemia during the first hour of occlusion were noted in 19 of the 34 dogs, but they did not persist for more than 20 minutes. The arrhythmias included sinus bradycardia and tachycardia, premature ventricular systoles, ventricular rhythm and rapid tachyarrhythmias. Fewer arrhythmias occurred in the next 2 hours.

Peak systolic pressure: Peak systolic pressure decreased 5 percent shortly after occlusion of the proximal left anterior descending coronary artery. At the end of 3 hours of occlusion, peak systolic pressure was reduced an average of 6 percent below the preocclusion control level. This reduction in blood pressure was about the same as that noted at the end of the 3 hours in the sham experiments. Study of individual animals revealed variations: 6 of the 34 dogs had a more significant reduction in pressure of 15 to 25 percent over the 3 hour period. The pressure increased gradually in six dogs (average 12 percent), and remained near control level in the remaining dogs. Peak systolic pressure was not reduced to less than 100 mm Hg in any animal during the 3 hour period of occlusion.

Left ventricular end-distolic pressure: Left ventricular end-diastolic pressure increased significantly (43 percent) immediately after occlusion. The mean

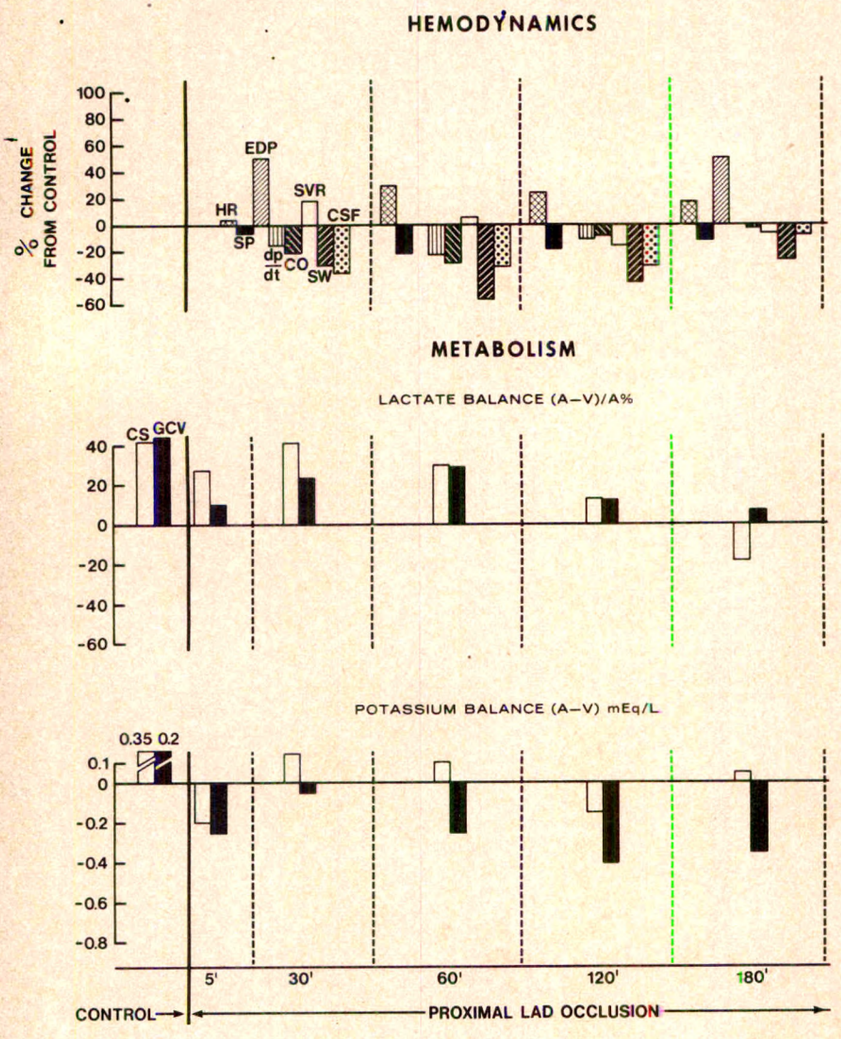

FIGURE 4. Hemodynamic and metabolic measurements during a control period and 3 hours of coronary occlusion in a dog. Hemodynamic function is reported as percent change from base-line control values. Control measurements were heart rate 124 beats/min; systolic pressure 139 mm Hg; left ventricular end-diastolic pressure 6 mm Hg; left ventricular dP/dt, 1,534 mm Hg/sec; cardiac output 2.1 liters/min; systemic vascular resistance 4,409 dynes sec cm^{-5}; stroke work 27 g-m/beat; and coronary sinus flow 75 ml/min. Immediately after occlusion there was a reduction in systolic pressure, left ventricular dP/dt, cardiac output, stroke work and coronary sinus flow. Coronary sinus flow values returned to normal during the occluded period in association with progressive improvement in all hemodynamic functions. However, there was progressive deterioration of lactic acid metabolism and potassium loss in the occluded and nonoccluded zones during the period of occlusion.

control value in this series was 7 mm Hg, and it reached 11 mm Hg at 3 hours of occlusion. By comparison, the sham series had smaller and nonsignificant changes in left ventricular end-diastolic pressure. Of the 34 dogs, 27 experienced an increase and 4 a decrease and 3 no change in left ventricular end-diastolic pressure during the course of occlusion. Only four dogs sustained a rise in left ventricular end-diastolic pressure above the level of 18 mm Hg after occlusion.

Maximal left ventricular dP/dt: Five minutes after occlusion, the maximal rate of rise of left ventricular pressure (dP/dt) had decreased significantly from a preocclusion mean control level of 2,840 to 2,270 mm Hg/sec (20 percent). Between 30 minutes and 3 hours of occlusion dP/dt fluctuated and averaged 2,310 mm Hg/sec at the end of the occlusion period. By comparison, the sham series had no significant change in dP/dt. Twenty of the study dogs had a decrease of more than 20 percent at the end of 3 hours of occlusion; the remaining 14 showed little change or a slight increase in dP/dt.

Cardiac output: Thirty minutes after occlusion, mean cardiac output had decreased 19 percent relative to the preocclusion control level. After this early reduction, cardiac output fluctuated somewhat, but at the end of the 3 hour occlusion period remained 15 percent below the control level. In the sham group, at equivalent measurement periods, cardiac output fluctuated near the control level. Fifteen of the 34 dogs sustained a reduction in cardiac output of more than 25 percent; in 8 dogs cardiac output occasionally exceeded the preocclusion control level.

Cardiac stroke work: Occlusion of the left anterior descending coronary artery caused an early reduction in mean stroke work (26 percent) which after 3 hours dropped further to 31 percent below control level. Increasing heart rate accounts for some of the reduction in stroke work. The sham group exhibited fluctuations, with a maximal reduction of 18 percent due to the increased heart rate. After occlusion, 11 of the 34 dogs had a sharp reduction in stroke work exceeding 45 percent, another 11 had a reduction exceeding 25 percent; only 1 dog showed an increase. Reduction in stroke work was not always related to increased heart rate; stroke work diminished 15 to 30

percent after occlusion in 15 animals that did not have an increased heart rate.

Systemic vascular resistance: Shortly after occlusion, mean systemic vascular resistance increased from 3,740 to 4,520 dynes sec cm^{-5} (21 percent). This early increase was followed by fluctuations, but at the end of the 3 hour occlusion period systemic vascular resistance was still 14 percent above control level. The sham group showed a transient mild increase at 30 minutes and 2 hours, but values returned to control levels at 3 hours. Immediately upon occlusion, 12 of the 34 dogs had a sharp increase of 59 percent in systemic vascular resistance. A more gradual increase occurred in 10 dogs. Systemic vascular resistance decreased in four dogs and remained unchanged in five.

Coronary sinus flow: During the control period, mean coronary sinus blood flow in 15 dogs was 125 ml/min, and after 3 hours was 108 ml/min. Six dogs sustained a marked and persistent decrease of 22 to 33 percent in coronary sinus flow immediately after occlusion. Five dogs showed no change, whereas four others had an initial decrease but a return to control levels at the end of 3 hours (Fig. 4). Four dogs had an increase in coronary sinus flow during the occlusion period (Fig. 3). In two of these, the increased flow was related to increased heart rate.

Coronary arterial pressure and sampling distal to the occlusion: Coronary arterial pressure dropped sharply as a result of acute occlusion of the left anterior descending coronary artery. Progressive changes in coronary arterial pressure were noted. It was necessary to analyze the individual diastolic and systolic phases in coronary arterial pressure. Although the average systolic coronary arterial pressure increased from 42 to 50 mm Hg, individual experiments revealed fluctuations ranging from 35 to 70 mm Hg. Diastolic coronary arterial pressure increased from 16 to 18 mm Hg during 3 hours of acute occlusion, indicating little increase in the preexisting collateral circulation.

Blood sampled from beyond the area of occlusion was found to be arterialized with a mean oxygen saturation of 90 to 96 percent.

II. Metabolism

Lactate balance: In the nonoccluded segment, mean lactate balance (arteriovenous [a-v] difference/arterial [A] × 100%) was 34.4 percent during the preocclusion control period and decreased significantly to 23.5 percent after 5 minutes of occlusion of the proximal left anterior descending coronary artery (Fig. 2). Subsequently, the lactate balance fluctuated but, after 3 hours of occlusion, mean lactate balance in this zone was 23.7 percent. This suggests that the metabolism of the nonoccluded segment is adversely affected. Study of individual lactate balances of the nonoccluded area revealed that, immediately after occlusion, abnormal lactate metabolism occurred in 22 animals and lactate production in 7; lactate balance remained normal in 5 dogs.

Lactate balance in the occluded zone decreased significantly from a mean preocclusion control level of 25 percent to 6.1 percent within 5 minutes, and to −1.0 percent after 30 minutes of occlusion (Fig. 2). The latter value indicates lactate production in the occluded zone. Lactate balance of this zone fluctuated thereafter, and after 3 hours of occlusion was +7.8 percent. In 17 dogs the occluded zone exhibited lactate production early in occlusion and in 17 others, abnormal lactate metabolism.

The metabolic derangements of the occluded zone were more pronounced than those of the nonoccluded segment. The difference between the lactate balance in the two segments was statistically significant throughout the period of occlusion.

Myocardial potassium balance: a-v difference fluctuated somewhat during the 3 hour occlusion period, but a loss of potassium was noted in both zones (Fig. 2 to 4). Within the first 5 minutes of occlusion, there was a large potassium loss (greater than 0.5 mEq/liter), from the occluded segment in 11 dogs and from the nonoccluded zone in 2. In the remaining 3 hours of occlusion, potassium loss from the occluded zone occurred in 17 dogs and from the nonoccluded segment in 12. The greatest potassium loss from any occluded segment was 1.35 mEq/liter. In this animal there was no significant potassium loss from the nonoccluded zone. The greatest potassium losses were noted from both occluded and nonoccluded zones when arrhythmias occurred.[1]

Oxygen extraction: Regional oxygen arteriovenous differences were measured in the zones of the left ventricle perfused by the left anterior descending and left circumflex coronary arteries. Control oxygen extraction values were 57 percent in both areas (Table I). During the initial period of occlusion, there was a 6 to 8 percent increase in oxygen extraction relative to control values in both regions and, for the remaining 3 hours of occlusion, oxygen extraction values in both zones remained at about this level.

III. Histopathology

After 3 hours of occlusion of the left anterior descending coronary artery, the hearts were excised and examined, and sections were subsequently stained with hematoxylin-eosin for light microscopy study. Sections of myocardium from the anterior left ventricles exhibited only mild peripheral vascular congestion and a faint suggestion of increased eosinophilic staining of myocardial fibers. Nuclei and individual fibers appeared intact. There was no inflammatory response. Sections of the myocardium from one dog showed mildly increased granularity of myocardial fibers, and, at the periphery, occasional margination of leucocytes was seen.

Discussion

The closed chest Corday-Lang model[1] used in this series provided simultaneous data on hemo-

dynamic status and regional metabolism during 3 hours of acute occlusion of the proximal left anterior descending coronary artery.

Regional Metabolic Effects

Metabolic data gathered simultaneously from the occluded as well as the nonoccluded segments of the left ventricle are essential to the study of regional effects of coronary occlusion. Many studies have used the coronary sinus effluent to represent events occurring in the ischemic zone after coronary occlusion.[3-5] However, data based on blood sampling in the coronary sinus alone represents mixed venous drainage from both the left anterior descending and left circumflex arteries and therefore cannot be used to study regional mechanisms.[6,7] Our new method of separately sampling the great cardiac vein draining the segment perfused by the left anterior descending coronary artery allowed assessment of the metabolic function of that zone, while simultaneous sampling from the coronary sinus represented function of the nonoccluded myocardium mainly perfused by the left circumflex artery.[1]

When myocardial lactate balance is less than 20 percent, most investigators consider that this is a sign that abnormal lactate metabolism has occurred.[4,5] There is general agreement that negative balance signifies lactate production. In the current study, data obtained from the occluded zone revealed a significant metabolic derangement within 5 minutes of occlusion, as evidenced by a reduction in mean lactate balance from 35.0 to 6.1 percent. The lactate balance in the occluded zone deteriorated further to production levels and remained abnormal throughout the occlusion period.

An unexpected and important finding was that the nonoccluded zone showed significant reduction of lactate extraction within a few minutes of occlusion in 65 percent of the dogs (Table I, Fig. 2). Lactate balance remained depressed thereafter, and in 20 percent of the animals reached production levels (Fig. 2 to 4). For example, in three animals, lactate balance decreased from a normal extraction value of 30 to 45 percent to production levels of −15 to −19 percent (Fig. 3, 4). Recently investigators[9] have reported other indications of metabolic dysfunction of the nonoccluded region when they observed a marked reduction in adenosine triphosphate (ATP) and creatine phosphate (CP) levels after occlusion.[9] A direct correlation was noted between the depressed ATP levels and reduced left ventricular stroke work and dP/dt. It was postulated that this metabolic derangement is caused by a depletion of tissue catecholamines.[10]

Detailed comparison of data from the occluded and nonoccluded zones revealed that, although abnormal lactate metabolism and potassium loss occurred in both areas, a far greater derangement occurred in the occluded region. Our experiments seldom confirmed the direct quantitative relation between potassium loss and lactate production reported by other investigators.[4,8] Our data also contrast with those of other workers who demonstrated similar potassium and lactate levels in the great cardiac vein and coronary sinus.[7] They found a significant increase only in a local vein draining a small area of infarction in the zone perfused by the left anterior descending coronary artery. We believe that the effluent from a small infarction is substantially diluted by other venous flow from nonoccluded myocardium before reaching the great cardiac vein, precluding true metabolic assessment of the ischemic zone by great cardiac vein or coronary sinus sampling. By contrast, our study reports data from a more extensive ischemic region secondary to occlusion of the proximal left anterior descending coronary artery. Also, the effluent from the ischemic zone (great cardiac vein) is temporarily separated during sampling from the nonischemic region (coronary sinus) by inflating a balloon within the great cardiac vein. Thus, measurements of metabolic function from the two zones are distinctly regional. Although some overlap or shunting might be expected between the occluded and nonoccluded segments and might possibly affect measurements during temporary occlusion of the great cardiac vein, we believe that such contamination was minimal because we noted distinct differences in both potassium and lactate balances between the two zones.

Hemodynamic Events

The mean hemodynamic response during the first 5 to 30 minutes of occlusion of the left anterior descending coronary artery was a significant change in cardiac function: left ventricular end-diastolic pressure increased 43 percent, maximal left ventricular dP/dt decreased 20 percent, cardiac output decreased 19 percent, stroke work was reduced 26 percent, and systemic vascular resistance increased 21 percent. These changes were significant relative to the sham animal results. Further alterations in mean hemodynamic measurements up to 3 hours of occlusion were relatively minor; however, heart rate increased (18 percent) and systemic vascular resistance showed a partial return in the direction of control values. Study of individual dogs revealed differing and often conflicting trends. Thus, systemic vascular resistance would occasionally markedly increase or decrease during the 3 hours of occlusion, and the related change in left ventricular afterload may be responsible for the fluctuations noted in cardiac output and other hemodynamic variables. Left ventricular end-diastolic pressure remained increased and maximal left ventricular dP/dt depressed in most cases, but there were instances of reduced left ventricular end-diastolic pressure and alterations in left ventricular dP/dt that could not be correlated with other indexes of cardiac function. We conclude that the dynamics of the occlusion process cannot be fully comprehended by studying only the statistical results, and that consideration of individual case data is equally important in studies of occlusion mechanisms.

Coronary Circulation

In contrast to previous reports that a compensatory increase in coronary arterial blood flow occurs in

the nonoccluded segment of the myocardium during occlusion of an adjoining artery,[11,12] our preliminary regional coronary flow measurements revealed that venous blood drainage from the nonoccluded myocardium was actually reduced 10 to 15 percent after occlusion of the left anterior descending artery.[13] This discrepancy may be due to differences in measurement techniques and preparations used. A reduction in coronary flow could be due to reflex angiospasm, associated hypotension or increased coronary resistance resulting from compensatory hypercontraction causing increased muscle tension in the nonoccluded segment. We postulate that the metabolic derangements in the nonoccluded myocardium can be attributed to a combination of reduced regional coronary blood flow, in association with increased oxygen demands due to regional compensatory hypercontraction or increased left ventricular afterload.

Study of the progressive alterations in coronary arterial pressure measured distal to the occlusion of the left anterior descending artery led to detailed analysis of the systolic and diastolic phases of coronary arterial pressure. Only the diastolic phase of coronary arterial pressure can be used as an approximate index of the coronary collateral circulation. In many instances, the level of coronary arterial pressure depends on the pressure differential between anastomosing occluded and nonoccluded coronary arteries. In contrast, the systolic pulse of coronary arterial pressure is greatly influenced by ventricular muscle tension and exhibits fluctuations that tend to correspond to those in left ventricular pressure during the occlusion period. It is well known that during arrhythmias coronary arterial pressure reflects systemic pressures.[14] When the level of systemic pressure drops critically during arrhythmias, this coronary arterial pressure, which reflects the coronary collateral circulation to the occluded zone, is also critically reduced.

In this study, the diastolic phase of coronary arterial pressure increased only slightly, suggesting that coronary collateral circulation distal to the occlusion did not improve significantly. Our metabolic studies indicate that the collateral circulation is unable to alleviate the metabolic dysfunction of the occluded region.

Clinical implication: Occlusion of the proximal left anterior descending coronary artery usually resulted in significant and immediate, although sometimes temporary, deterioration in global mechanical and hemodynamic function. At the same time, metabolic function was depressed in both nonoccluded and occluded myocardial regions and an anaerobic state often supervened in the latter zone. In the ensuing 3 hours of observation, mean measurements of metabolic and hemodynamic function generally did not show significant improvement. There were considerable fluctuations suggesting the influence of dynamic processes. Individual experiments occasionally showed progressive improvement in mechanical function even though regional metabolism remained depressed or an anaerobic state developed (Fig. 3, 4). Conversely, deterioration in hemodynamic function was noted in some experiments in which metabolism remained normal (Fig. 4). Thus, metabolic and mechanical functions after coronary occlusion may follow opposing trends. Examination of individual factors such as heart rate and systemic vascular resistance suggested that each of these can cause derangements of either mechanical or metabolic function in specific experiments. In some instances the heart appeared to contract well and maintain hemodynamic status during short periods of anaerobic metabolism. A phase lag between metabolic and mechanical myocardial events may be implicated. The period of these observations was admittedly limited and, therefore, the significance of such mechanical-metabolic dissociations is not clear.

It is possible that measurement of mechanical function of the left ventricle locally, rather than "globally," might clarify these idiosyncrasies and explain mechanisms. Unfortunately, our series did not provide sufficient data on regional mechanics. To adapt the Corday-Lang model to perform regional measurements of myocardial forces and strains, we are attempting to develop more suitable miniature gauge instrumentation.[1]

An increase in heart rate was generally observed, and short-lived arrhythmias were occasionally encountered in the early period of occlusion. These arrhythmias were often, but not always, associated with increased potassium efflux from both normal and occluded segments. The anaerobic state did not seem to be associated with onset of arrhythmias; however, spontaneous arrhythmias usually induced severe metabolic dysfunction of both the ischemic and nonischemic myocardium.

The most striking finding in this study was the significant metabolic dysfunction, manifested by disturbed regional lactate metabolism and potassium loss, that occurred in the nonoccluded segment after the occlusion period. This segment is usually assumed to remain normal after a remote coronary occlusion. In the study reported next,[15] involving the same model and 3 hours of occlusion of the proximal left anterior descending coronary artery, subsequent reperfusion caused an immediate and major "washout" of metabolites from the nonoccluded as well as the occluded zones. Further study is required to determine whether this "washout" related to the accumulation of metabolites in the cell and interstitial spaces during occlusion.

The depressed metabolic function of the nonoccluded segment may be attributed, in part, to the tentatively established decrease in regional coronary flow. However, it might be due to increased oxygen demands in this zone resulting from increased left ventricular afterload caused by greater aortic impedance or compensatory hypercontraction of the nonoccluded zone, or both. Thus, the coronary blood supply of the nonoccluded segment may be insufficient to maintain normal metabolic function. The latter observations are in accord with recent reports indicating metabolic derangements of adenosine triphosphate and creatine phosphate in the noninfarcted

zones,[9,10] as well as decreased coronary arterial flow in the remote nonoccluded segment.[16]

Simultaneous oxygen percent saturation measurements in the aorta and in the temporarily separated two venous drainages, from the occluded and nonoccluded segments of the left ventricle, indicated an approximate 6 to 8 percent increase in oxygen extraction during the occlusion in both myocardial segments. These measurements may be interpreted differently for the two regions: (1) In the occluded zone, the ischemic myocardium attempts to extract more oxygen to compensate for the significantly reduced coronary flow; and (2) in the nonoccluded zone, the higher level of extraction may be attributed to a compensatory hypercontraction of the nonoccluded segment,[17,18] increased left ventricular afterload associated with increased systemic vascular resistance, and relative ischemia and metabolic derangements caused by a decreased regional coronary flow.

These metabolic alterations in myocardial function in the nonoccluded area during coronary occlusion should be considered important because, after 3 hours of occlusion, damage in the central occluded zone may be irreversible, whereas myocardium may be salvageable in the border zone and also in the all-important nonoccluded segment, now known to be jeopardized. The genesis of cardiogenic shock is still unknown. It is possible that the compromised metabolic function of the still viable myocardium described here may play a principal role in establishing a series of vicious cycles. When a shock state occurs, pharmacologic and circulatory assist interventions may restore function to this nonoccluded segment, whereas function of the occluded zone cannot be restored. This new concept of the involvement of the nonoccluded segment may provide a better understanding of the genesis and treatment of cardiogenic shock.

Acknowledgment

We thank Olga Diner, Myles Prevost, Willis Curtis Pea, John Friedman, Elaine Calmenson, Jules Osher, and Jeanne Bloom for their technical assistance. We also appreciate the assistance of Dr. Glenn Langer as consultant on this study.

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Consequences of Reperfusion After Coronary Occlusion

Effects on Hemodynamic and Regional Myocardial Metabolic Function

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Hemodynamic and regional metabolic measurements were obtained in seven closed chest dogs during a control period, 3 hours of coronary occlusion and 5 hours of reperfusion. Reperfusion resulted in intermittent ectopic arrhythmias in five dogs and severe shock in two. It usually caused increases in heart rate, coronary sinus flow and maximal isovolumetric rate of rise in left ventricular pressure (dP/dt), which were associated with a decrease in systemic pressure, left ventricular end-diastolic pressure, systemic vascular resistance and stroke work. A transitory increase in cardiac output occurred. Global myocardial oxygen consumption, which was reduced during occlusion, increased with reperfusion. Reperfusion induced abnormal lactate metabolism and myocardial potassium loss in the previously occluded area and often in the nonoccluded segment as well. Histopathologic changes of accelerated necrosis, reactive hyperemia and hemorrhage were often noted after reperfusion.

These studies indicate that reperfusion after 3 hours of occlusion caused serious abnormalities in hemodynamic states, metabolic function and morphologic features of the heart.

Although the progressive alterations in cardiac function after coronary occlusion have been studied[1], only limited data are available on the effects of reperfusion on metabolic and mechanical function.[2-4] A common goal of investigators is to determine whether injury to myocardial tissue can be reversed by reperfusion after various periods of coronary occlusion. Debate persists about the criteria of myocardial viability after coronary occlusion, particularly with regard to temporal relations.[5-12] At low temperatures and drastically reduced metabolic demands, myocardial tissue may survive for as long as 24 hours without its coronary supply, whereas at normal body temperatures, the damage caused by occlusion for 20 to 180 minutes might not be reversed by reperfusion.[5,9] Clearly, viability depends upon many factors whose elucidation requires sophisticated measurements and improved models. Insight into mechanisms of viability should be derived by studying the metabolic and hemodynamic indexes of myocardial function. It is of great importance to determine whether cardiac dysfunction can be reversed by reperfusion. The scope and time course of regional and global myocardial alterations during coronary occlusion and subsequent reperfusion are of interest to the cardiac surgeon and clinician who need to establish the time during which revascularization might still restore cardiac function and viability.

Viability of cardiac muscle has largely been studied by histopathologic and histochemical methods.[7-9] However, because study of tissue morphology alone does not adequately resolve the issue of myocardial viability, further extensive studies are deemed necessary to fill in the gaps in our knowledge and to correlate the pathologic, mechanical, hemodynamic, electrophysiologic and metabolic effects of

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TABLE I

Hemodynamic Data in Seven Dogs (means ± standard error of the mean)

		Occlusion					Reperfusion						
	Control	5 Min	30 Min	1 Hr	2 Hr	3 Hr	Imm	30 Min	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
HR	109 ±9	112 ±7	123 ±19	114 ±19	97 ±8	100 ±7	107* ±5	141* ±23	136*† ±10	151*† ±12	159*† ±14	169* ±13	171*† ±16
SP	136 ±8	126 ±9	128 ±9	129 ±8	132 ±9	133 ±7	131 ±6	126 ±8	126 ±7	123† ±6	117† ±8	119 ±9	107† ±11
EDP	6 ±1.5	7 ±1.4	9 ±1.7	10 ±1.3	11† ±1.3	11† ±2.0	10 ±1.7	8 ±0.8	9 ±1.5	7 ±2.1	7 ±1.4	7 ±1.3	6 ±1.7
dP/dt	2740 ±260	2200† ±265	2355† ±215	2100† ±220	1855† ±245	1840† ±215	1825† ±200	1970† ±210	2000† ±215	2100† ±305	2310† ±300	2535 ±315	2270 ±330
CO	3.3 ±0.3	2.7 ±0.2	2.5 ±0.3	2.3† ±0.4	2.3† ±0.4	2.3† ±0.4	3.2 ±0.8	2.3† ±0.3	2.8 ±0.6	2.4 ±0.4	2.5 ±0.4	2.4 ±0.3	2.1† ±0.3
SVR	2720 ±150	3150 ±215	3565† ±257	4430† ±550	4325† ±535	4365† ±500	3300* ±760	4125† ±460	3790 ±565	3815 ±575	3510* ±330	3525* ±345	3640*† ±350
SW	47 ±7.6	35 ±10.6	35 ±7.6	36 ±8.8	37 ±7.8	34 ±7.0	45 ±4.9	29† ±5.6	33 ±10.9	24† ±5.0	24† ±4.9	19*† ±4.3	17*† ±3.9
CSF	179 ±18	142 ±34	128 ±27	128 ±28	120 ±32	117† ±27	...	136 ±24	131 ±25	153 ±26	144 ±22	145 ±15	160 ±22

* $P < 0.05$ relative to 3 hour occlusion value.

† $P < 0.05$ relative to preocclusion control value.

CO = cardiac output (liters/min); CSF = coronary sinus flow (ml/min); dP/dt = maximal rate of rise of left ventricular pressure (mm Hg/sec); EDP = left ventricular end-diastolic pressure (mm Hg); HR = heart rate (beats/min); Imm = immediately on reperfusion; SP = systolic pressure (mm Hg); SVR = systemic vascular resistance (dynes sec cm^{-5}); SW = stroke work (g-m/beat).

reperfusion after coronary occlusion. Recent studies of reperfusion used epicardial S–T segment mapping in the open chest and measurement of alteration in myocardial enzymes to demonstrate the extent of myocardial injury.[3,13,14]

In this study we attempted to establish the effects of reperfusion on hemodynamic and regional metabolic functioning of the left ventricle. We believe that applicable information can be derived from controlled animal experiments when adequate physiologic simulation is feasible. The main questions we hope to answer are how reperfusion affects the occluded and nonoccluded segments of the myocardium, and whether adverse functional and morphologic derangements occur that might complicate the course of myocardial recovery.

Methods and Procedures

The study was carried out in seven anesthetized, closed chest dogs weighing 30 to 35 kg. The application of intracoronary balloon catheters for occlusion of a specific coronary artery and for simultaneous measurement of hemodynamic status, myocardial blood flow and regional myocardial metabolism has been described.[1,15] Blood volume depleted through blood sampling and fluid losses was replaced by infusion of physiologic saline solution at a rate of 75 to 100 cc/hour.

Acute occlusion of the proximal left anterior descending coronary artery was performed through inflation of an intracoronary balloon at the tip of a special no. 4F catheter.[15] The methodology of this intracoronary occlusion procedure and the collection of blood samples from the great cardiac vein and coronary sinus, and simultaneous measurement of hemodynamics, were fully described as the Corday-Lang model.[15] Deflation of the balloon and removal of the intracoronary catheter provided total reperfusion of the coronary artery. Regional myocardial, metabolic and coronary flow measurements were achieved by the previously described technique of temporary separation of venous compartments through inflation of a balloon placed in the great cardiac vein.[1,15]

Cardiac function was measured in a preocclusion control period, after a 30 minute stabilization period, at intervals of 5, 30, 60, 120 and 180 minutes during occlusion of the left anterior descending coronary artery, and 1, 30, 60, 120, 180, 240, and 300 minutes after reperfusion. After completion of 3 hours of occlusion and 5 hours of reperfusion, each heart was excised. After gross examination to insure the absence of arterial or venous thrombosis, the area of gross infarction was delineated and tissue sections of the occluded and nonoccluded zones were prepared for light microscopy using standard and specialized stains.

Results

Hemodynamic data of seven closed chest dogs obtained during a preocclusion control period, 3 hours of proximal occlusion of the left anterior descending coronary artery and 5 hours of reperfusion are presented in Table I. Percent changes from the preocclusion control values are shown in Figures 1 through 4; both mean statistical results and individual data

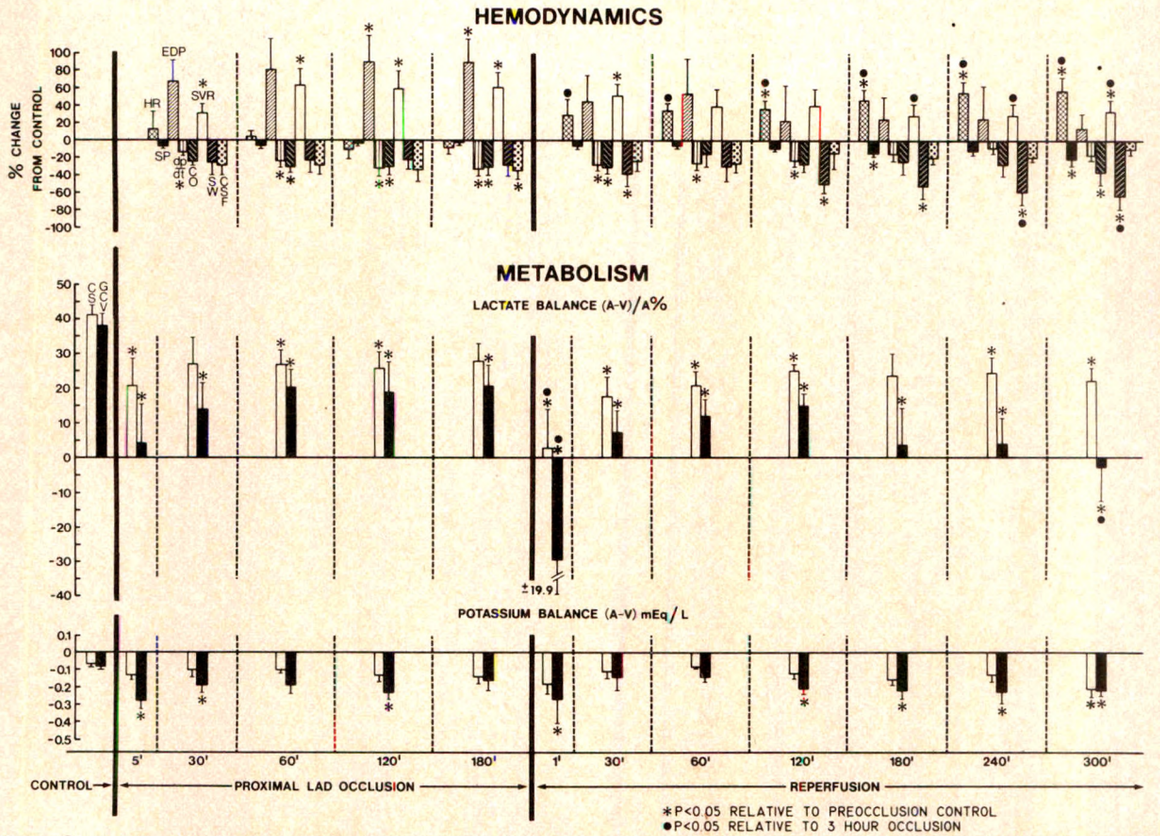

FIGURE 1. Composite statistical summary (seven dogs) of hemodynamic and metabolic measurements (lactate and potassium balances) during a control period, 3 hours of occlusion and 5 hours of reperfusion. The **top bar graph** demonstrates the percent change from the base-line control values. Control measurements were heart rate (HR) 109 beats/min; systolic pressure (SP) 136 mm Hg; left ventricular end-diastolic pressure (EDP) 6 mm Hg; left ventricular dP/dt (dp/dt) 2,740 mm Hg/sec; cardiac output (CO) 3.3 liters/min; systemic vascular resistance (SVR) 2,720 dynes sec cm^{-5}; stroke work (SW) 47 g-m/beat; coronary sinus flow (CSF) 179 ml/min. Significant changes during the occlusion period were an increase in left ventricular end-diastolic pressure and systemic vascular resistance and progressive decreases in cardiac output, left ventricular dP/dt, stroke work and coronary sinus flow. With reperfusion there was a further decrease in stroke work because of increased heart rate, and systolic pressure, cardiac output, systemic vascular resistance and left ventricular end-diastolic pressure also decreased. Left ventricular dP/dt increased despite the reduced cardiac output. Five minutes after coronary occlusion there was a change from normal lactate extraction to abnormal lactate metabolism in the occluded and nonoccluded segments. During the reperfusion period there was an initial lactate washout from both segments. Three to 5 hours after reperfusion there was further deterioration as evidenced by lactic acid production in the occluded zone although the coronary flow had returned toward normal. There was a large potassium loss from the occluded area and a smaller loss from the nonoccluded zone almost immediately after occlusion. The potassium loss continued 2 to 5 hours after reperfusion. (A-V)/A = arteriovenous difference/arterial; CS = coronary sinus; GCV = great cardiac vein; LAD = left anterior descending coronary artery.

are presented. Hemodynamic fluctuations necessitated averaging of measurements during periods of arrhythmias.

The measurements include heart rate, peak systolic aortic pressure, left ventricular end-diastolic pressure, maximal isovolumetric rate of rise in left ventricular pressure (dP/dt), cardiac output, systemic vascular resistance, cardiac stroke work and total coronary sinus flow. Regional metabolic data during control, coronary arterial occlusion and reperfusion periods are reported for myocardial segments perfused by the left anterior descending and left circumflex coronary arteries, respectively. These regional measurements, presented in Table II, include percent lactate balance, ([arteriovenous (a-v)/arterial] × 100), a-v difference in potassium balance, percent oxygen extraction (arteriovenous oxygen saturation) and total myocardial oxygen consumption. The progressive alterations in lactate and potassium balances are shown in Figures 1 through 6. Coronary sinus flow measurements and left ventricular myocardial oxygen consumption measurements were performed in five of the seven dogs. Individual experiments are also presented (Fig. 2 to 4). Residual myocardial potassium and histopathologic findings and their significance are reviewed in the Discussion.

Hemodynamics

Heart rate: During the 3 hours of occlusion of the left anterior descending coronary artery, heart rate fluctuated and reached a value 8 percent below the preocclusion control value (Fig. 1, Table I). Immedi-

TABLE II

Metabolic Data in Seven Dogs (means ± standard error of the mean)

		Occlusion					Reperfusion						
	Control	5 Min	30 Min	1 Hr	2 Hr	3 Hr	Imm	30 Min	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
Lactate balance													
Nonoccluded ([Ao-CS]/Ao × 100)	41.0 ±2.9	20.9* ±8.2	29.4 ±6.6	27.3* ±4.3	26.0* ±5.0	28.1 ±5.4	2.8*† ±11.6	18.2* ±5.8	21.5* ±4.4	25.3* ±1.8	23.7 ±6.6	24.7* ±4.5	22.2* ±3.8
Occluded ([Ao-GCV]/Ao × 100)	38.7 ±3.6	4.3* ±11.5	14.2* ±7.9	20.1* ±5.3	19.3* ±8.9	20.9* ±6.3	−29.8*† ±19.9	7.4* ±6.6	12.1* ±5.0	15.1* ±3.7	3.7* ±11.0	4.1* ±7.8	−2.9*† ±10.0
Potassium balance													
Nonoccluded (Ao-CS)	−0.07 ±0.02	−0.13 ±0.03	−0.10 ±0.04	−0.10 ±0.02	−0.13 ±0.04	−0.14 ±0.04	−0.18 ±0.06	−0.11 ±0.04	−0.08 ±0.01	−0.12 ±0.03	−0.16 ±0.03	−0.13 ±0.04	−0.21* ±0.05
Occluded (Ao-GCV)	−0.08 ±0.02	−0.28* ±0.05	−0.19* ±0.04	−0.19* ±0.05	−0.23* ±0.04	−0.16 ±0.06	−0.27 ±0.14	−0.14 ±0.08	−0.14 ±0.03	−0.21* ±0.03	−0.22* ±0.05	−0.23* ±0.07	−0.22* ±0.03
Oxygen saturation													
Nonoccluded (Ao-CS) (%)	54.7 ±4.7	60.0 ±3.3	58.4 ±2.8	57.9 ±3.2	57.0 ±3.4	59.1 ±3.5	49.9 ±5.2	56.1 ±4.1	56.4 ±4.5	59.9 ±4.2	58.7 ±3.2	58.8 ±3.2	60.9 ±4.9
Occluded (Ao-GCV) (%)	55.4 ±4.8	60.8 ±3.0	61.5 ±2.7	60.9 ±3.8	60.6 ±2.5	61.0 ±2.7	40.6 ±6.0	52.5 ±4.7	54.1 ±5.5	59.6 ±4.6	59.8 ±4.0	60.1 ±4.5	58.6 ±5.5
Total myocardial oxygen consumption‡ (ml/min per 100 g)	10.1 ±1.0	...	8.0 ±1.2	7.4 ±1.1	6.4* ±1.2	6.7* ±1.3	...	7.5 ±1.1	7.3 ±1.0	9.8 ±1.5	8.9 ±1.4	8.5 ±0.8	9.2 ±0.9

* $P < 0.05$ relative to control value.
† $P < 0.05$ relative to 3 hour occlusion value.
‡ no. = 5.
Ao = aorta; CS = coronary sinus; GCV = great cardiac vein.

ately after reperfusion, heart rate rose to 29 percent, and after 5 hours was 57 percent above the control value. This corresponds to a 41 percent and 71 percent rise, respectively, above the 3 hour occlusion level.

Individual results were variable. Heart rate increased markedly during the occlusion period in one dog, decreased in three and remained near control level in three. After 5 hours of reperfusion, heart rate was substantially increased in six of the seven dogs (Fig. 3, 4). In six dogs, reperfusion caused arrhythmias consisting principally of sinus tachycardia, multifocal premature systoles, slow ventricular rhythm and intermittent and sustained ventricular tachyarrhythmias.

Peak systolic pressure: Mean peak systolic pressure decreased 6 percent below control level 5 minutes after occlusion of the left anterior descending coronary artery and then remained near control level throughout the 3 hour period of occlusion. Reperfusion caused a gradual further decrease in this mean pressure until it was 21 percent below control level at the end of 5 hours of reperfusion, or 20 percent below the value obtained at 3 hours of occlusion.

During occlusion, the systolic pressure decreased in two dogs, increased in one and remained essentially unchanged in the other four. After 5 hours of reperfusion, a substantial reduction in peak systolic pressure occurred in three of the seven dogs, and in two reached shock levels, defined as a reduction in both systolic pressure and cardiac output to 30 percent below control levels (Fig. 4).

Left ventricular end-diastolic pressure: Mean left ventricular end-diastolic pressure was 6 mm Hg in the control period and increased 89 percent after 3 hours of occlusion. Reperfusion resulted in a decrease to near control level at the end of the 5 hour period (Fig. 1, Table I). This represents a 45 percent decrease from the 3 hour occlusion level.

In four of the seven dogs, left ventricular end-diastolic pressure remained increased after occlusion, and in one dog it increased to a high value of 31 mm Hg (Fig. 4). The increased values usually returned to normal after reperfusion. In three dogs they remained substantially below control levels during the reperfusion period even though fluid replacement of 75 to 100 cc/hour was maintained throughout the 8 hour period.

Maximal left ventricular dP/dt: Maximal left ventricular dP/dt dropped gradually to 33 percent below control level at the end of 3 hours of occlusion of the left anterior descending coronary artery. After 5 hours of reperfusion, there was a rise to 23 percent above the 3 hour occlusion value, corresponding to 17 percent below control level (Fig. 1, Table I).

During occlusion, maximal left ventricular dP/dt was substantially depressed in five of the seven animals. After 5 hours of reperfusion, it returned to nor-

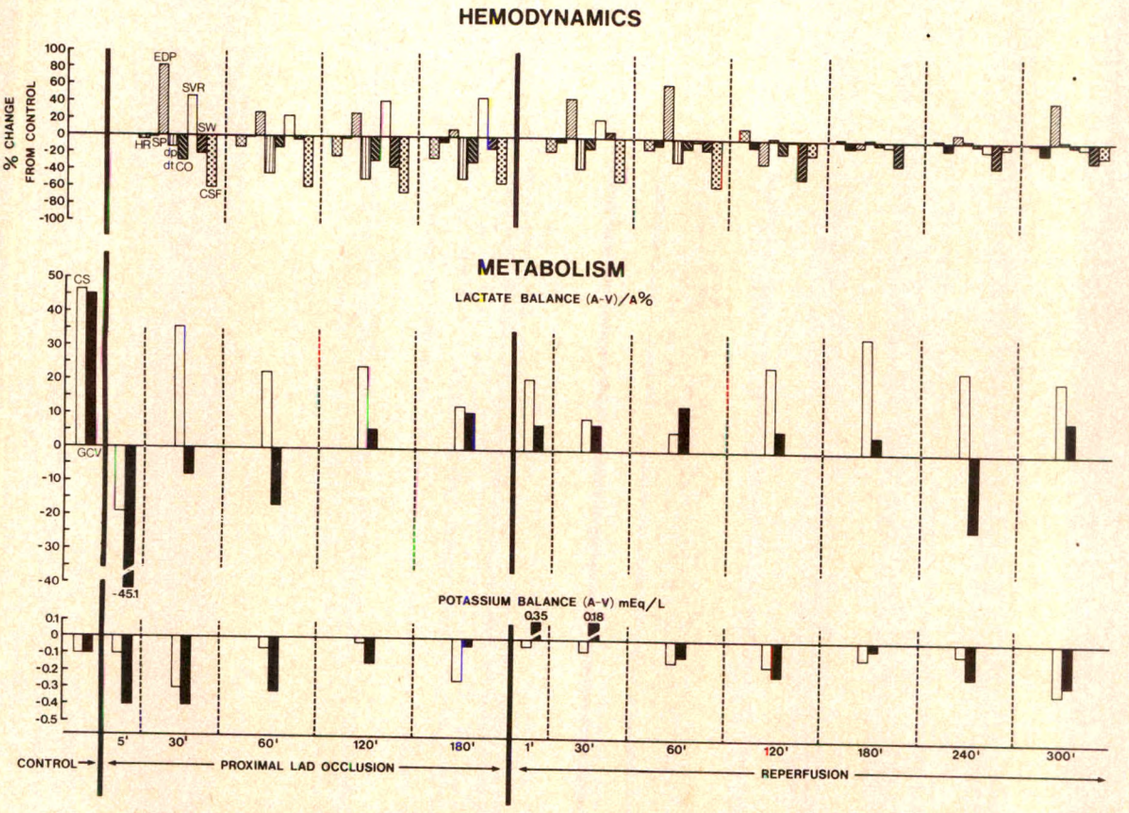

FIGURE 2. Hemodynamic and metabolic data obtained in a dog during 30 minute control period, after 3 hours of occlusion of the left anterior descending coronary artery and 5 hours of reperfusion. The control hemodynamic measurements were heart rate 118 beats/min; systolic pressure 131 mm Hg; left ventricular end-diastolic pressure 6 mm Hg; left ventricular dP/dt 3,400 mm Hg/sec; cardiac output 2.83 liters/min; systemic vascular resistance 2,835 dynes sec cm^{-5}; stroke work 35 g-m/beat; coronary sinus flow 203 ml/min. Immediately upon occlusion lactic acid production occurred in both the occluded and nonoccluded segments and there was a significant potassium loss in the occluded zone. There was some improvement in the lactic acid and potassium balances over the next 3 hour period. However, heart rate, left ventricular dP/dt, cardiac output, stroke work and coronary sinus flow were reduced as systemic vascular resistance increased. With reperfusion there was no lactate or potassium washout. During the next 5 hours of reperfusion hemodynamic function improved; however, lactic acid production and potassium loss returned in the occluded zone. Abbreviations as in Figure 1.

mal in three dogs (Fig. 2) and deteriorated further in four others (Fig. 4). A disparity was occasionally noted between maximal left ventricular dP/dt, cardiac output and left ventricular end-diastolic pressure, particularly during experiments in which shock occurred.

Cardiac output: The mean cardiac output was reduced 30 percent after 3 hours of occlusion. Immediately after reperfusion it averaged 11 percent below control level, and after 5 hours of reperfusion it was reduced to 36 percent below control level, that is, an 8 percent decrease relative to the value at the end of the occlusion period (Fig. 1, Table I).

Two animals sustained a 55 to 65 percent reduction in cardiac output, became markedly hypotensive and experienced shock after reperfusion (Fig. 4). Two other dogs that did not become hypotensive had a reduction in cardiac output of 41 and 51 percent, respectively.

Systemic vascular resistance: Mean systemic vascular resistance increased 16 percent immediately after occlusion and increased to 63 percent above control level after 3 hours of occlusion. During 5 hours of reperfusion, systemic vascular resistance fluctuated downward to about 33 percent above control level, or 17 percent below the final occlusion value.

In four normotensive dogs, systemic vascular resistance increased 32 to 80 percent above control level at 5 hours of reperfusion. In two dogs, it dropped below control level. In one dog, the decrease in systemic vascular resistance was associated with a reduction in cardiac output (Fig. 2); in the other, cardiac output showed an increase (Fig. 3). Of the two dogs with shock, one had a reduction and the other an increase in systemic vascular resistance (Fig. 4).

Stroke work: Stroke work was reduced after 3 hours of occlusion of the left anterior descending coronary artery and decreased further to 64 percent below control level at the end of the 5 hour reperfusion period, a 50 percent reduction below the 3 hour occlusion level. This reduction was usually associated with an increase in heart rate (Fig. 1, Table I).

Two animals that experienced shock sustained a marked decrease in stroke work, to 84 and 88 percent, respectively, below control values (Fig. 4).

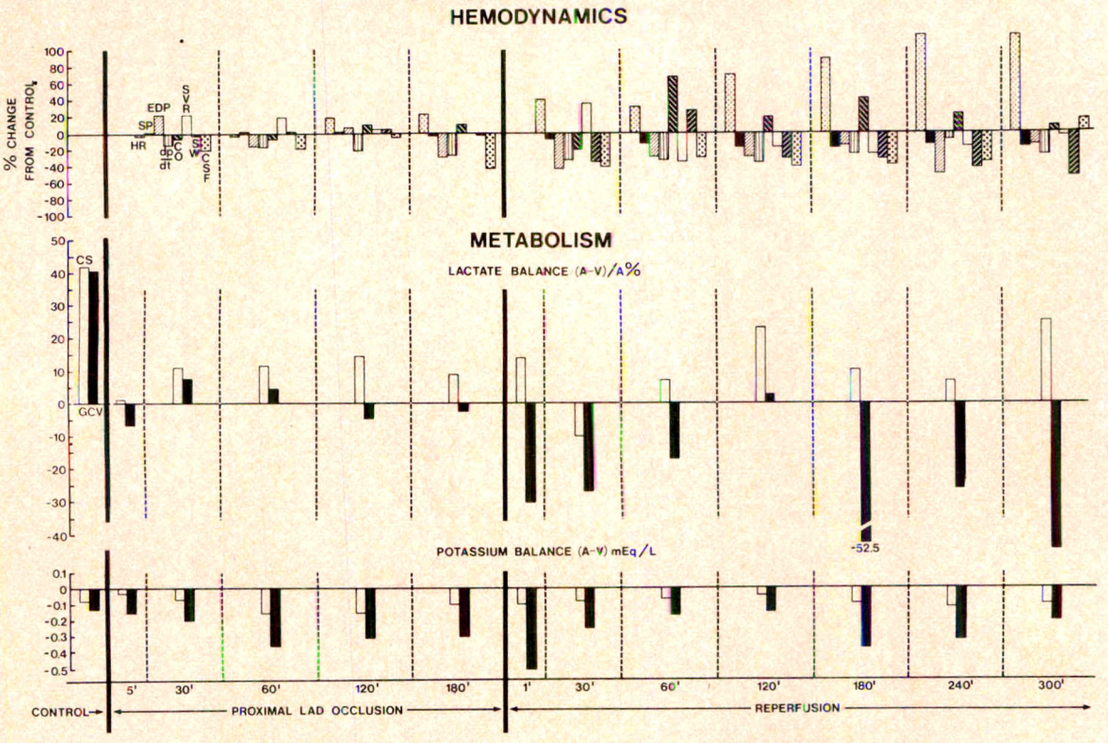

FIGURE 3. Hemodynamic, lactate and potassium measurements in a dog during a 30 minute control period, 3 hours of occlusion of the left anterior descending coronary artery, and 5 hours of reperfusion. Base-line hemodynamic data during preocclusion control were: heart rate 83 beats/min, systolic pressure 167 mm Hg, left ventricular end-diastolic pressure 5 mm Hg, left ventricular dP/dt 3,736 mm Hg/sec, cardiac output 3.4 liters/min, systemic vascular resistance 2,820 dynes sec cm^{-5}, stroke work 74 g·m/beat, and coronary sinus flow 182 ml/min. Immediately upon occlusion, abnormal lactate metabolic and potassium loss occurred in the occluded and nonoccluded regions. At the end of 3 hours of occlusion, coronary sinus flow was reduced 40 percent. Left ventricular dP/dt was reduced, whereas cardiac output was maintained slightly above control levels. After reperfusion, a drastic increase in lactate production and potassium loss occurred in the occluded zone, which persisted throughout the 5 hours of reperfusion. Potassium loss and abnormal lactate metabolism occurred to a lesser degree in the nonoccluded zone after reperfusion. At the end of 5 hours of reperfusion, cardiac output was maintained near control levels, but stroke work was sharply reduced because of a rapid heart rate. Coronary sinus flow returned to slightly above control values.

Coronary sinus flow: Total coronary sinus flow was measured in five dogs. It was reduced 21 percent below control level in the early occlusion period and at the end of 3 hours was reduced to 36 percent below control level. After 30 minutes of reperfusion the mean coronary sinus flow was 24 percent below control level. Total coronary sinus flow 5 hours after reperfusion was still 11 percent below the preocclusion control value, which is a 37 percent improvement compared to the value at the end of occlusion (Fig. 1, Table I). In two dogs the coronary sinus flow was increased 10 and 27 percent, respectively, above control levels, immediately after reperfusion, thus suggesting that reactive hyperemia had occurred.

Metabolism

Lactate balance ([a-v difference/arterial] × 100 (%)): Five minutes after occlusion of the left anterior descending coronary artery there was a significant decrease in lactate balance in the occluded region from a preocclusion mean control level of 39 to 4 percent, indicating severely deranged lactate metabolism (Fig. 1, 5, Table II). The nonoccluded segment also exhibited a significant initial decrease in lactate extraction, from 41 to 21 percent. The subsequent 3 hours of occlusion were characterized by some fluctuations in both zones. Three hours after occlusion, lactate balance in the occluded zone increased to 21 percent and in the nonoccluded zone to 28 percent. Immediately upon reperfusion, there was a marked reduction to −30 percent in the occluded zone and to +3 percent in the nonoccluded region. These sudden changes are thought to represent washout of accumulated metabolites. After 5 hours of reperfusion the previously occluded zone exhibited lactate production with a balance of −3 percent; the nonoccluded zone at this time showed a balance of +22 percent (Fig. 1, 5, Table II).

In three dogs, 3 hours of occlusion of the left anterior descending coronary artery resulted in a substantial reduction of lactate balance in the nonoccluded zone (2 to 20 percent) (Fig. 3, 4). All seven dogs exhibited instances of abnormal lactate metabolism, and three showed lactate production in the occluded zone (Fig. 2 to 4). After 5 hours of reperfusion, three of the seven dogs had substantial lactate production in the previously occluded area (Fig. 3); one dog had improved lactate balance. Five of the seven showed improved lactate extraction in the nonoccluded region (Fig. 2 to 4).

Potassium balance (a-v difference): Five minutes of occlusion of the left anterior descending coro-

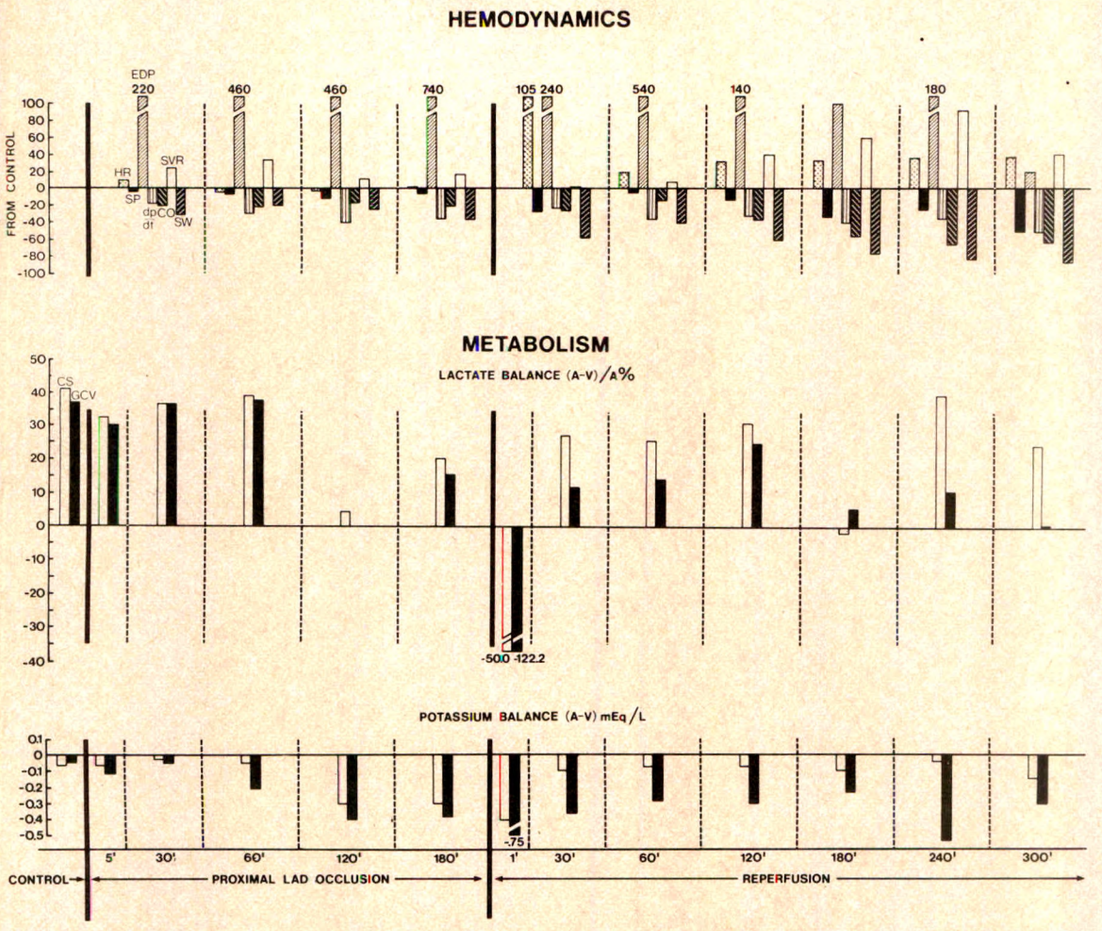

FIGURE 4. Hemodynamic, lactate and potassium data obtained in a dog during a control period, 3 hours of occlusion of the left anterior descending coronary artery and 5 hours of reperfusion. The bars represent percent changes from the control values which were: heart rate 130 beats/min; systolic pressure 151 mm Hg; left ventricular end-diastolic pressure 3 mm Hg; left ventricular dP/dt 2,565 mm Hg/sec; cardiac output 4.7 liters/min; systemic vascular resistance 2,096 dynes sec cm^{-5}; stroke work 67 g-m/beat; coronary sinus flow 229 ml/min. In the late occlusive period there was a large potassium loss from both occluded and nonoccluded zones. With reperfusion, a large lactate and potassium washout occurred. The potassium loss from the occluded segment continued over 5 hours of reperfusion. Shock occurred 3 hours after onset of reperfusion as exhibited by decreases of 40 percent in systolic pressure and 50 percent in cardiac output. Abbreviations as in Figure 1.

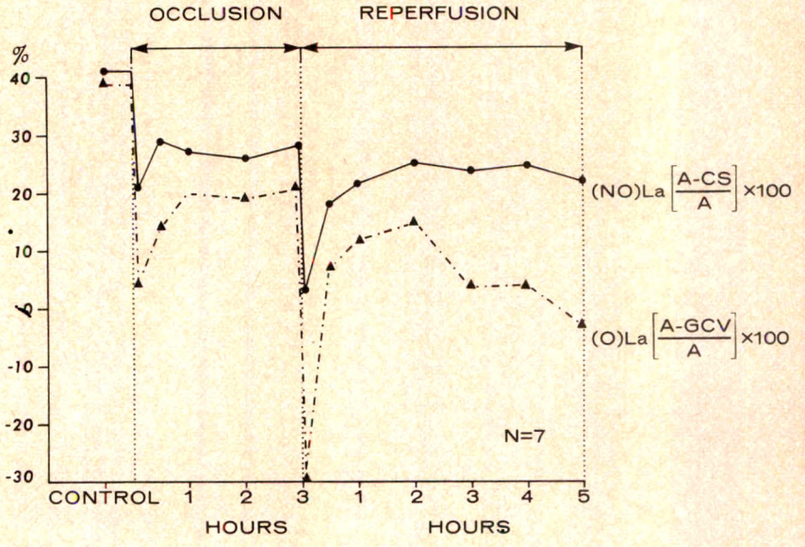

FIGURE 5. Average lactate balances in seven dogs, measured in nonoccluded (NO) (**solid line**) and occluded (O) (**broken line**) areas during a control period, 3 hours of occlusion and 5 hours of reperfusion. Abnormal lactate metabolism occurred immediately after occlusion in both zones. Immediately after reperfusion the lactate acid level was reduced to −30 in the occluded zone and to +3 in the nonoccluded area. This probably represents a washout. During the last 2 hours of reperfusion, lactate metabolism deteriorated in the occluded zone. A = arterial; CS = coronary sinus; GCV = great cardiac vein; La = lactate.

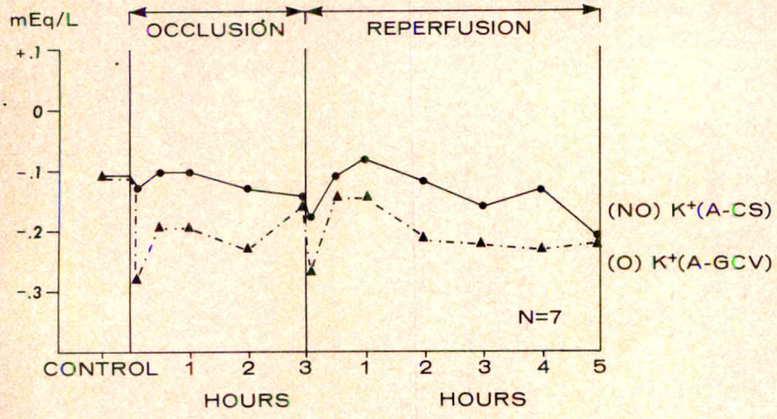

FIGURE 6. Average potassium balance in seven dogs, measured in nonoccluded (NO) (**solid line**) and occluded (O) (**broken line**) zone during a 30 minute control period, 3 hours of occlusion and 5 hours of reperfusion. A large immediate potassium loss from the occluded area after occlusion continued during the 3 hour period. After reperfusion there appeared to be an immediate washout of potassium and later a secondary potassium loss from both zones. Abbreviations as in Figure 5.

nary artery resulted in a significant reduction in potassium balance in the occluded zone from a mean control level of −0.08 to −0.28 mEq/liter, indicating a significant potassium loss (Fig. 1, 6, Table II). Meanwhile, there was only a slight change in the nonoccluded myocardium. During the remaining period of occlusion, a lesser rate of potassium loss occurred in the occluded zone, ranging from −0.16 to −0.23 mEq/liter. Immediately after reperfusion there was a significant loss of potassium from both zones, probably indicating a washout phenomenon. Thereafter, both regions exhibited a small loss of potassium.

A review of individual experiments showed that five of the seven dogs had a major potassium loss from the occluded zone during the first 5 minute period of occlusion, as great as 0.47 mEq/liter. At 3 hours of occlusion, four of the seven dogs had potassium loss from the occluded region, and two also had potassium loss from the nonoccluded zone. After reperfusion, the potassium loss in the previously occluded zone continued (Fig. 3, 4), but at lesser levels in three animals. Two animals began to lose potassium from both occluded and nonoccluded zones 5 hours after reperfusion (Fig. 2).

Regional oxygen extraction (a-v difference): During the 3 hour occlusion of the left anterior descending coronary artery, there was evidence of a slight (5 percent) increase in oxygen extraction in both the occluded and nonoccluded regions of the left ventricle (Table II). Except for a decreased extraction rate seen immediately upon reperfusion, the slightly increased extraction value in both zones was maintained with some fluctuations throughout the 5 hours of reperfusion.

Total myocardial oxygen consumption: Total myocardial oxygen consumption decreased progressively over the 3 hour period of occlusion from a mean of 10.1 to 6.7 ml/min per 100 g. During reperfusion, total oxygen consumption gradually increased to 9.8 ml/min per 100 g and then reached a level of 9.2 ml/min per 100 g at 5 hours of reperfusion (Table II). In two animals, oxygen consumption was reduced to 50 percent below control levels after 3 hours of occlusion, and then increased to 90 percent of control levels during reperfusion.

Pathologic Studies

Of the seven animals, six demonstrated myocardial infarction, five of which were transmural. These infarcts were located in the anterior left ventricular wall and the anterior apex. In two of the three dogs that had hypotension, infarcts were also seen in the posterior left ventricle. One dog that experienced shock associated with rapid tachycardia had no infarction. Four dogs, including the two hypotensive animals, demonstrated distinct microthrombi in the areas of infarction. Infarction was accompanied by various degrees of cellular necrosis and fragmentation of myofibrils, most pronounced in the dogs with shock. Intramyocardial vascular congestion (hyperemia) and hemorrhage accompanied the infarctions.

Discussion

Relation of Reperfusion and Viability

A review of experimental viability studies must consider the differences between the various preparations used.[2,6–10,12,16,17] The site and size of the coronary artery chosen for occlusion are of primary importance. The often quoted relation of the period of ischemia to the amount of necrosis found in the myocardial tissue was derived by Jennings et al.[7,17] from histopathologic studies of the posterior papillary muscles after temporary occlusion of the proximal circumflex branch of the left coronary artery. They reported an average zero percent of necrosis up to 20 minutes of occlusion, the percent of necrosis increasing rapidly to 42 percent at 30 minutes and then to 72.5 at 1 hour of occlusion. They did not attempt reperfusion after occlusion periods of more than 1 hour because the papillary muscles then exhibited hemorrhages, indicating that the vascular system was no longer intact and available for appropriate reperfusion. In evaluating such viability studies, consideration must be given to the fact that the coronary collateral circulation of the papillary muscles is minimal; thus, the results obtained in such prepara-

tions cannot be compared to results in segments of the heart with a more comprehensive collateral blood supply.

Extensive investigations in cats by Krug,[18,19] Enderle et al.[20] and Korb and Schlosser,[21] largely based on histopathologic and histochemical as well as enzymatic studies, indicate that irreversible myocardial cell damage occurred only after 75 to 90 minutes of temporary coronary arterial occlusion. Reperfusion, after a 90 to 120 minute occlusion period, caused only part of the previously occluded zone to be reperfused. In the early postocclusion reperfusion period there was little evidence of vessel damage, but subsequent reperfusion was associated with involvement of the microcirculation. Our studies noted thrombi in the microcirculation in four of the seven dogs. Irreversible myocardial tissue damage, characterized by increased tissue hydrogen ion content, reduced glycogen and intracellular and interstitial edema was reported.[11,18,22] A 3 hour temporary coronary occlusion with subsequent reperfusion generally led to transmural infarction. These investigators proposed that the primary factors causing irreversible damage were the duration of the temporary occlusion, disturbances engendered through reperfusion of previously ischemic regions, and the extent of the area perfused.

Reports by Hamer,[23] Maroko,[2] and Ginks[3] and their co-workers emphasized that coronary occlusion extending beyond 3 hours may be at least partially reversible through extended reperfusion. In particular, Hamer et al.[23] reported recovery of heart muscle after longer durations of occlusion followed by extended periods of reperfusion. A limited zone of damage may develop in the center of the ischemic region, chiefly at the subendocardial level, but since this damage need not bring about permanent global cardiac dysfunction, reperfusion could be beneficial.

Comment on the Present Technique

The current study involved only seven dogs, and a larger series is needed to arrive at a full description of the benefits as well as limitations of reperfusion. The regional metabolic measurements indicate a distinct separation of the ischemic and nonischemic compartments.[1,15] Separation is not total, in that our occlusion of the proximal left anterior descending coronary artery may leave a few arterial branches above the balloon intact, and there is a certain overlap of arterial supply and venous drainage from the major adjoining coronary systems. This could dilute the blood samples and lower the concentration of metabolites. Nevertheless, regional occlusion and reperfusion measurements usually provided a significant differentiation between data from the occluded and nonoccluded zones.[1,15]

The differing conclusions reported by various investigators may be attributed to inadequacies of most of the experimental preparations used to date. Thus, open chest preparations cannot be relied on because of the significant physiologic artifacts, such as depression in cardiac function relative to the closed chest model. Many experimental models of occlusion do not provide adequate control of the location and completeness of the occlusion. When the coronary occlusions are performed in the closed chest they are seldom reversible for the study of reperfusion. It has been suggested that extracoronary occluders or ligations may result in damage to pericoronary nerves, leading to unphysiologic artifacts.[24] Systematic regional flow and metabolic measurements, in addition to determinations of global cardiac function, during closed chest occlusions and reperfusions, have not been reported. Almost all data on the effects of reperfusion following coronary occlusion have been gathered in open chest dogs and are based on epicardial electrocardiographic mapping and serum creatine phosphokinase measurements in the ischemic and nonischemic zones.[2,3,25]

Questions are frequently raised about differences between the coronary circulation and cardiac function in dogs and man. One important factor, the coronary collateral circulation, was studied and discussed by us in a previous publication.[26] Our data indicated that, like the normal human heart, the normal beating dog's heart apparently has minimal functional collateral circulation. The preceding article[1] used the diastolic phase of pressure distal to the occlusion as an approximate index, and showed that acute coronary occlusion of 3 hours' duration failed to change significantly the extent of collateralization. Hence, for acute occlusions, we assume that the functional trends noted in the dog experiments should be applicable in man.

Myocardial Response to Occlusion and Reperfusion

A detailed study of the progressive alterations of cardiac function during 3 hours of intracoronary occlusion of the left anterior descending artery in 34 closed chest dogs has been reported in the preceding article.[1] The present series of seven dogs provides data on the progressive changes in hemodynamic status and regional metabolism during 5 hours of reperfusion after 3 hours of acute occlusion of the left anterior descending artery.

Effects of 3 hours of occlusion: In this series, 3 hours of occlusion of the left anterior descending coronary artery resulted in significant reduction in cardiac output, maximal left ventricular dP/dt, stroke work and coronary sinus flow, whereas left ventricular end-diastolic pressure and systemic vascular resistance increased significantly (Fig. 1, Table I). The hemodynamic results correspond to those outlined in the preceding article,[1] except that in this series a small decrease was noted in the heart rate at the end of the 3 hour period of occlusion. Before reperfusion, mean lactate balance of the occluded zone had reached 21 percent (control value 39 percent), whereas lactate balance in the nonoccluded zone was 28 percent (control value 41 percent). Potassium loss from the occluded zone as well as a lesser loss from the nonoccluded zone occurred during the occlusion

period. These metabolic derangements are in general accord with the previous more extensive occlusion study.[1] Data from this study confirm the striking metabolic derangement in the nonoccluded zone during the occlusion.[1,27,28]

During occlusion, total coronary sinus flow was decreased 36 percent below control level. Regional measurements indicate that coronary flow in the nonoccluded zone was decreased 10 to 15 percent below its preocclusion level.[1,15,29] This reduction in coronary flow differs from the results of others[30,31] and is ascribed by us to reflex coronary angiospasm, associated hypotension or increased resistance in the coronary circulation due to compensatory hypercontraction and increased muscle tension in the nonoccluded segment.[1] Recent reports[32] indicate similar reduction in remote coronary flow in the nonoccluded segment.

Myocardial oxygen extraction increased slightly during occlusion in both occluded and nonoccluded zones. Left ventricular oxygen consumption was reduced to 65 percent of the control level (Table II).

Effects of 5 hours of reperfusion—hemodynamics: The mean initial hemodynamic response to reperfusion compared with measurements after 3 hours of occlusion consisted of a significant 41 percent increase in heart rate, a small (5 percent) reduction in systolic pressure, a 27 percent reduction in left ventricular end-diastolic pressure, a 7 percent increase in maximal left ventricular dP/dt, a 5 percent decrease in systemic vascular resistance, a 15 percent decrease in stroke work and a 16 percent increase in coronary sinus flow. After 5 hours of reperfusion, heart rate increased 71 percent, peak systolic pressure decreased 20 percent, left ventricular end-diastolic pressure was reduced by 45 percent, maximal left ventricular dP/dt increased 23 percent, cardiac output decreased by 8 percent, systemic vascular resistance decreased 17 percent, and stroke work was sharply reduced by 50 percent. Coronary sinus flow increased 37 percent to near preocclusion control levels.

An important trend noted in this series was the sharp rise in heart rate that occurred immediately after reperfusion and persisted for 5 hours in five dogs. In addition, intermittent arrhythmias occurred immediately after reperfusion in six of the seven dogs and frequently reappeared during the reperfusion period. The elevated heart rate and particularly the arrhythmias may have contributed to the abnormal hemodynamic and metabolic function during reperfusion in three dogs. One animal had sinus tachycardia, with an increase in heart rate from 115 to 224 beats/min, followed by cardiogenic shock. Autopsy did not reveal necrosis of the myocardium. Another animal (Fig. 2) had a normal heart rate and improved hemodynamic status after reperfusion, but after 1 hour of reperfusion abnormal lactate metabolism occurred intermittently in both nonoccluded and occluded segments. Pathologic study of this animal indicated multiple foci of necrosis in the center of the occluded zone. These data suggest a dissociation between hemodynamic and metabolic function and lack of correlation with morphology.

The predominant finding in three of the seven animals was declining mechanical function during 5 hours of reperfusion, that is, decreased blood pressure, reduced cardiac output and sharply diminished stroke work.

Mean coronary sinus flow increased immediately upon reperfusion, and after 5 hours rose to a value 11 percent below the preocclusion control level, that is, a 37 percent rise relative to the end of the 3 hour occlusion period. The slightly lower value for coronary flow may be due to a reduced coronary perfusion pressure. There was essentially no change in oxygen extraction during the five hours of reperfusion. Myocardial oxygen consumption was restored to 91 percent of the control level during reperfusion, that is, a 33 percent rise relative to the final occlusion value (Table II).

Metabolism: The immediate effect of reperfusion was a marked "washout" of lactic acid and potassium from the previously occluded zone and often also from the nonoccluded region (Fig. 1, 3 to 6). Washout may be taken as additional evidence of an abnormal regional metabolism in both zones during the preceding period of occlusion. Our findings suggest that metabolites accumulated in the interstitial spaces and were washed away by sudden reperfusion. It cannot be ascertained whether the initial effects of reperfusion include improvement or deterioration in metabolism, because the sudden washout may mask or distort the measurement of regional metabolic function.

Measurements of regional myocardial metabolism after 5 hours of reperfusion revealed a remarkable but often intermittent deterioration of the previously occluded zone in six of seven dogs. Thus, the occluded zone that exhibited a 21 percent lactate extraction at 3 hours of occlusion, demonstrated lactate production (−3 percent) during reperfusion (Fig. 1, 5). A further small intermittent reduction in lactate balance was often noted in the nonoccluded zone. During reperfusion, potassium loss occurred intermittently in both occluded and nonoccluded regions (Fig. 1, 6).

A survey of the individual experiments indicates variations in data and trends during the reperfusion period. Various lactate and potassium measurements did not always show a correspondence, and there were instances (Fig. 2 to 4) in which lactate extraction decreased, but potassium loss increased and vice versa. The dynamics of the reperfusion process are illustrated in Figures 2 and 4, which show considerable fluctuations in both metabolic and hemodynamic function. A dissociation of metabolic and mechanical trends was observed in many instances, showing either improved hemodynamics in the presence of depressed metabolism (Fig. 2) or mechanical dysfunction in the presence of stable or improved myocardial metabolism. A phase lag between meta-

bolic and mechanical events may play a role in this dissociation, but other mechanisms could be involved.

Residual Tissue Analysis and Histopathology

Tissue analysis for residual myocardial potassium concentration taken at autopsy corroborated the finding that the previously occluded segment has less residual potassium than the nonoccluded myocardium. The borderline zone between segments has an intermediate potassium level (Fig. 7).

Microscopic sections of the heart were stained with hematoxylin basic fuchsin picric acid in addition to standard hematoxylin-eosin. Necrosis and fragmentation of the myofibrils, microthrombi and hemorrhages that were not evident in dogs after 3 hours of occlusion[1] were observed after reperfusion. This finding suggests that reperfusion accelerated changes of necrosis. It is postulated that the hemorrhages are related to reperfusion in areas that have sustained damage to the microvasculature or in which hyperemia has occurred. The degree to which microthrombi interfere with the effectiveness of reperfusion is not clear, but these lesions are probably of fundamental importance.

The hematoxylin basic fuchsin picric acid stain was reported to have affinity for myocardial cells altered by ischemia.[33] We found that reperfusion, which was evidenced by the microscopic finding of reactive hyperemia, caused a loss of stainability of this agent, although hematoxylin-eosin stain revealed ischemic necrosis and microthrombi. Patchy stainability with hematoxylin basic fuchsin picric acid was usually retained only in areas that demonstrated microthrombi. We postulate that this stain is bound by the accumulated ischemic metabolites that are washed away during reperfusion. It thus appears that after reperfusion this stain is not helpful in delineating the extent of damage in the previously occluded zone.

Clinical Implications

Our study leads to the conclusion that reperfusion may not be capable of reversing hemodynamic and metabolic disorders induced by 3 hours of acute coronary occlusion. In fact, it may cause serious deterioration of metabolic and hemodynamic function. Only two animals showed persistent improvement of hemodynamic indexes. Two animals experienced cardiogenic shock. Four animals showed the largest loss of potassium starting 4 to 5 hours after onset of reperfusion. At that time the previously occluded area revealed a severe reduction in lactate balance while the nonoccluded zone showed less metabolic dysfunction. Whether a shorter or longer period of reperfusion, either gradual or sudden, would alter these cardiac functions remains to be clarified. Correlative autopsy studies revealed that reperfusion accelerated morphologic alterations and caused reactive hyperemia, microthrombi and hemorrhages that were not evident at the end of 3 hours of occlusion.

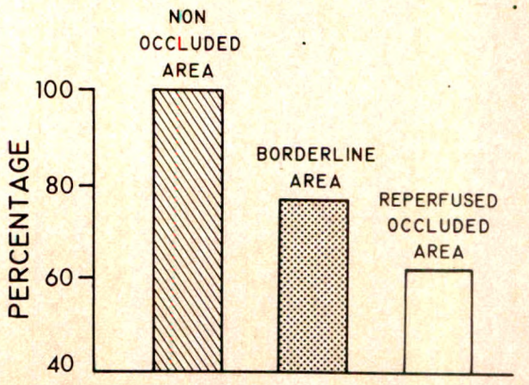

FIGURE 7. Comparison of myocardial residual potassium measurements in percent of potassium from the nonoccluded zone. Heart muscle from the occluded segment had a substantially lower potassium concentration (62 percent) than the nonoccluded segment. The borderline area potassium content was also distinctly less (77 percent) than the concentration in the nonoccluded zone.

This investigation clearly indicates that reperfusion after 3 hours of acute coronary occlusion may have a detrimental effect on both the viability and mechanical and metabolic function of the myocardium. It is possible that reperfusion after shorter intervals—for example, 1 or 2 hours—of occlusion may not cause accelerated necrosis and deterioration of cardiac function. Investigations of shorter periods of occlusion followed by reperfusion are currently underway.

The next logical question concerns the beneficial or detrimental effects of various periods of reperfusion on an admittedly precariously balanced myocardium following 3 hours of occlusion of the proximal left anterior descending coronary artery. One of our most interesting observations, made possible through the regional measurements of the new model, concerns the "washout" that immediately follows the reperfusion. Individual experiments show considerable variability and differences in the magnitude of this lactate and potassium "washout" in both occluded and nonoccluded segments. We believe that the "washout" of accumulated metabolites can serve as an indication of the degree of metabolic dysfunction and possible ischemic damage caused by a 3 hour period of coronary occlusion, and we are now correlating histopathologic data with lactate washout measurements. It might thus be reasoned that the myocardium could have been in a precarious state even though systemic compensatory factors such as increased systemic vascular resistance may have prevented or postponed total circulatory collapse. In the presence of damage to the ischemic region and its microcirculation, a sudden burst of reperfusion and associated reactive hyperemia might be the cause of the patchy hemorrhages. The ischemic damage and reactive hyperemia, in turn, could cause additional metabolic derangements that would be reflected in increased or prolonged "washout." To minimize myocardial damage during reperfusion, we

are studying modifications to make reperfusion more gradual or staged, as well as systems that combine reperfusion with administration of pharmacologic agents such as mannitol, allopurinol or cortisone. The large washout of potassium during sudden reperfusion could well be the reason for tachyarrhythmias[34] which may cause serious derangements in cardiac function and contribute to the genesis of vicious cycles leading to ventricular fibrillation.[33-37]

We do not yet know whether a more prolonged reperfusion period could have averted the dire metabolic and morphologic consequences we observed. Cases have been cited in which an akinetic segment remained inert for several hours after 3 hours of occlusion but became almost fully contractile after days or weeks.[23] On the other hand, we frequently noted a severe potassium loss or development of shock 4 to 5 hours after reperfusion, suggesting that extension of the reperfusion period might generate further deterioration and shock.

A recent report[38a] contends that when coronary bypass was performed in patients immediately after acute coronary occlusion, the mortality rate was three times higher than if acute infarction was not present. Another human study[38b] indicated that the mortality rate was 80 percent when coronary bypass was performed on the first day after occlusion, 38 percent 2 to 8 days after occlusion, 13 percent 8 to 30 days after occlusion and only 6 percent 31 to 60 days after occlusion. It is not known how many patients in the latter study had cardiogenic shock and this factor could have weighted the results. Such studies suggest that revascularization might have a detrimental effect in the first week after acute coronary occlusion. Successful attempts to correct cardiogenic shock by revascularization of the heart by coronary bypass immediately after occlusion have been reported.[39] Of course, total circulatory assistance, which was used during such operations with frequent intermittent periods of coronary reperfusion while the heart was at rest, may provide essential nutrition to the myocardium and restore function of the vital nonoccluded segment and thus overcome the shock state.

Sudden death due to ventricular fibrillation frequently occurs in patients whose coronary arteries are not occluded. We have found a high frequency of ventricular fibrillation in animals after reperfusion of the coronary arteries. This observation was first reported by Tennant and Wiggers in 1935.[40] The question arises whether the sudden release of coronary angiospasm or lysis of a thrombus in a coronary artery may set up reperfusion disorders described in this study such as sudden electrolyte washout, anaerobic metabolism and loss of mechanical function, which could precipitate resistant ventricular fibrillation. This study contributes new knowledge about the precursors and mechanisms of sudden death which might lead to more adequate therapy of the nation's number one health problem.

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Deleterious Effects Due to Hemorrhage After Myocardial Reperfusion

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The effect of coronary reperfusion on evolving myocardial infarction was examined in 16 conscious dogs. Coronary arterial occlusion was produced by inflating an exteriorized balloon cuff, and reperfusion was initiated 5 hours later by deflating the cuff. Infarct size calculated from 24 hour serial serum creatine phosphokinase (CPK) values was compared to infarct size predicted from log normal curves best fit to initial 5 hour serial CPK changes. With sustained occlusion, predicted and observed infarct size correlated closely (r = 0.94, no. = 11). Reperfusion produced two disparate effects. In nine dogs, observed infarct size was less than predicted, reflecting 42 ± 6 percent (standard error) salvage of myocardium. In seven dogs, observed infarct size exceeded predicted size by more than 100 percent. Thus, reperfusion resulted in extension of myocardial infarction in 44 percent of the animals. Extension of infarction was associated with myocardial hemorrhage. Hemoglobin content in biopsy specimens from the center of the infarct was 10 times greater in the animals with extension of infarction than in those with myocardial salvage. Thus, reperfusion is not without hazard during evolving infarction in the conscious dog; although it frequently diminishes ischemic injury, it may precipitate myocardial hemorrhage and extension of infarction.

The availability of saphenous vein bypass grafting for patients with acute myocardial infarction has accentuated the need to examine the effects of myocardial reperfusion on infarct size. We have recently shown that reperfusion early after coronary arterial occlusion reduces the extent of myocardial necrosis in anesthetized dogs[1,2]; however, its effectiveness may depend on how soon it is performed after occlusion.

This experimental study was designed to determine whether infarct size is influenced by reperfusion initiated 5 hours after coronary occlusion, an interval analogous to one that might be used in clinical settings. The experiments were performed in conscious animals to obviate effects of anesthesia. We[3,4] have previously shown that analysis of serial serum creatine phosphokinase (CPK) changes provides an accurate estimation of infarct size in conscious dogs and that there is a close correlation and linear relation between infarct size* determined in this manner and infarct size determined by analysis of myocardial CPK depletion (r = 0.96). Recently, we[5] used curve fitting techniques to predict infarct size 5 hours after coronary occlusion in the conscious dog and found that this value correlated closely with ultimate infarct size resulting from a sustained coronary occlusion (r = 0.96, no. = 11). In the present investigation we used the same technique to predict infarct size 5 hours after occlusion, immediately before reperfusion. Predicted infarct size was compared to infarct size calculated from all serum CPK values measured during the 24 hour interval after coronary occlusion.

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* For convenience this term will be used to refer to the extent of myocardial injury reflected by myocardial CPK depletion, since we have previously demonstrated that myocardial CPK depletion and independent indexes of necrosis correlate closely.[3]

To assess the effects of reperfusion on the extent of myocardial injury, we used an experimental preparation that eliminated the need for concurrent surgery. Coronary occlusion was produced in 16 conscious dogs by inflating a balloon cuff that had been placed around the left coronary artery 7 to 10 days previously. Reperfusion was initiated 5 hours later by deflating the balloon. Infarct size was predicted 5 hours after occlusion, immediately before reperfusion, on the basis of early serum CPK changes; this value was then compared to observed infarct size calculated from serum CPK changes measured during the ensuing interval. Thus, each animal served as its own control. Myocardial tissue was considered salvaged when observed infarct size was smaller than predicted. Infarction was considered extended when observed infarct size exceeded that predicted. Contrary to our initial expectation, only nine animals (56 percent) showed salvage of myocardial tissue after reperfusion; the remaining seven had apparent extension of infarction. Extension of infarction was consistently associated with myocardial hemorrhage. The methods used provide information about the total mass of myocardium undergoing ischemic injury and do not distinguish between extension of infarction beyond the original "border" of the ischemic area and extension of infarction due to more intensive damage within the original "border."

Methods

Animal Preparations

Sixteen animals were anesthetized with sodium thiamylal (10 mg/kg body weight), and anesthesia was maintained with 0.5 percent Fluothane®. A silastic balloon cuff was placed loosely around the left anterior descending coronary artery through a left thoracotomy.[6] A polyvinyl catheter continuous with the balloon cuff was exteriorized and secured to the skin. A jugular venous catheter was inserted for obtaining blood samples, and the animals were permitted to recover from operation. Seven to 10 days after operation all animals were premedicated with lidocaine, 1 mg/kg intravenously. Coronary arterial occlusion was produced by inflating the balloon. No sedation was required. Blood samples were obtained immediately before coronary occlusion for determination of base-line serum CPK activity. Additional samples were obtained hourly for 24 hours. Five hours after coronary occlusion the balloon was deflated to initiate reperfusion. Lidocaine, 1 mg/kg intravenously, was again administered, immediately before reperfusion. Twenty-four hours after coronary occlusion each animal was anesthetized with sodium pentobarbital. Through a left thoracotomy, the coronary artery was incised distal to the cuff to determine whether the vessel was patent and whether free reflow had been established. The heart was excised and left ventricular biopsy specimens were taken from the nonischemic posterior myocardium and from the center of the infarct (estimated grossly). The remaining myocardial tissue was used for preparation of whole ventricular homogenates.[4]

Calculation of Infarct Size

Determination of infarct size from analysis of serial serum CPK changes: Infarct size was determined, as previously described,[4] by analysis of serial serum CPK changes based on the equation $dE/dt = f(t) + kdE$, where E = enzyme activity, kd = the fractional disappearance rate and t = time in minutes after the initial increase in serum CPK. Rearrangement of terms, integration, multiplication by the distribution volume of CPK and division by the proportion of myocardial CPK depleted appearing in serum provides an expression used to calculate the amount of CPK depleted from myocardium based on measurement of serial serum CPK changes. Since myocardial CPK depletion is directly proportional to infarct size,[3,4] infarct size can also be calculated.[4]* We refer to infarct size calculated by this method as observed infarct size. Its value is calculated from changes in serum CPK activity during the entire 24 hour interval after coronary occlusion. This interval is selected because after 24 hours myocardial CPK depletion is minimal.[4]

Prediction of infarct size from projected serum CPK curves: We have previously shown that infarct size can be predicted 5 hours after coronary occlusion in the conscious dog on the basis of serum CPK values obtained from the projected portion of the best fit curve derived from early data relating serum CPK changes to time. Serum CPK changes after sustained coronary occlusion conform to a log normal function. Accordingly, the best fit curve conforming to this general function can be obtained from data obtained during the first 5 hours after the initial enzyme increase by conventional curve fitting techniques.[5] Predicted infarct size is calculated from CPK values on the projected portion of the best fit curve. After sustained coronary occlusion, observed and predicted infarct size differ by less than 5 percent, and the correlation coefficient between the two is 0.96.[5] Predicted infarct size derived from projected CPK values can be used to assess the efficacy of an intervention initiated after the prediction has been made because the projected best fit curve is independent of events occurring after the first 5 hours. Since the fraction of CPK released into serum of CPK depleted from myocardium is a critical parameter in the calculation of infarct size, we assessed the relation between CPK depleted from myocardium and the amount of CPK released into blood. The amount of CPK released was calculated from serial serum CPK changes. The value for myocardial CPK depletion, calculated from CPK activity in normal myocardium, total left ventricular CPK content and left ventricular weight, was used to calculate infarct size as previously described.[4]

Tissue Preparations

The animals were anesthetized, the beating heart was rapidly excised, and blood was quickly drained from the ventricular cavities. The left ventricle including its septal wall was isolated, washed three times for 1 minute each in cold saline solution (4° C), blotted dry with a paper towel and weighed. Full wall thickness biopsy specimens were taken from nonischemic regions of the posterior left ventricular free wall and from ischemic regions of the center of the infarct. Supernatant fractions at 16,000 g were prepared from individual biopsy specimens and from the remainder of the left ventricle by mincing the tissue, homogenizing it in 0.25 M sucrose containing 0.001 M neutralized sodium ethylenediaminetetinetic acid with 0.001

* Infarct size = $K \sum_{0}^{T} (\Delta E/\Delta T + kd\ \bar{E})\Delta t$ where kd = CPK disappearance rate; E = serum CPK, $\bar{E}$ = mean CPK during Δt, K = [(BW)(DV)]/[(D) (CPK_N-CPK_I)], BW = body weight, DV = distribution volume, and D = depleted/released CPK, CPK_N and CPK_I = CPK in normal and ischemic myocardium.

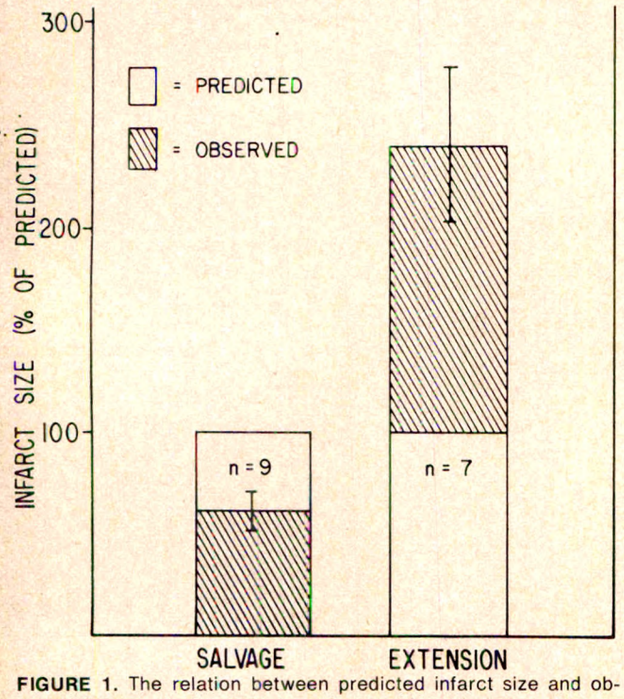

FIGURE 1. The relation between predicted infarct size and observed infarct size in conscious dogs subjected to coronary occlusion and reperfusion 5 hours later. Predicted infarct size in nine animals exhibiting salvage of myocardium averaged 27 ± 6 (standard error) CPK-g-eq compared to 14 ± 4 in seven animals exhibiting extension of infarction.

M mercaptoethanol, and centrifuging as previously described.[4]

Lysates were prepared from red blood cells. Cells were separated by centrifugation at 3,000 g for 10 minutes, washed three times in cold saline solution (4° C) and hemolyzed in distilled water.

Biochemical Procedures

Protein was measured by the biuret procedure.[7] Creatine phosphokinase (CPK) activity in serum, myocardial supernatant fractions and red cell lysates were assayed spectrophotometrically[3,8] with 50 μliter aliquots in a final assay volume of 1.050 ml. Samples with activity exceeding 0.1 international units (IU)/ml were diluted with 0.01 M trishydroxymethylaminomethane (Tris), pH 7.4, containing bovine serum albumin 0.2 percent (Tris-BSA). CPK activity was expressed in international units per milliliter or per milligram of protein.

Hemoglobin was assayed spectrophotometrically[9] in supernatant fractions of myocardium from the center of the infarcts and from nonischemic regions. To determine whether adenylate kinase, adenosine triphosphate (ATP), or glucose-6-P were influencing apparent CPK activity, experiments were performed in which creatine phosphate was omitted from the CPK reaction medium. CPK isozymes were assayed by electrophoresis on cellulose acetate for 65 minutes at 250 volts with 5 μliter serum samples from animals with and without apparent salvage of myocardium after reperfusion. Isozymes were quantified by fluorescent scanning techniques.[10]

Results

Effect of reperfusion on infarct size: Reperfusion 5 hours after coronary occlusion in conscious dogs modified infarct size (Fig. 1). In nine dogs, observed infarct size was appreciably less than that predicted. Hence, reperfusion modified infarct size favorably and led to salvage of 42 ± 6 percent (mean ± standard error) of myocardial tissue expected to undergo infarction in the absence of a favorable intervention. The absolute values for salvaged myocardial tissue ranged from 0.6 to 29.0 CPK-g-eq (mean 11 ± 3). Predicted infarct size in this group averaged 27 ± 6 CPK-g-eq. Thus, in this group of nine animals representing 56 percent of those subjected to reperfusion, the intervention led to substantial salvage of myocardial tissue. In the remaining seven dogs subjected to reperfusion, observed infarct size was 100 percent greater than that predicted. Thus, reperfusion resulted in apparent extension of infarction. The absolute values for myocardial damage exceeding that predicted ranged from 0.6 to 56 CPK-g-eq (mean 24 ± 9). Predicted infarct size in this group averaged 14 ± 4 CPK-g-eq, although this value was not significantly less ($P = 0.13$) than that in the animals with salvaged myocardial tissue.

The ratio of CPK depleted from myocardium to CPK released into the circulation varied by less than 10 percent (no. = 9). Results with the methods used would not be influenced by the rate of release of CPK from myocardial tissue but would be influenced by a change in the proportion of released CPK appearing in blood. Since animals with apparent salvage of myocardium and those with extension of infarction exhibited comparable proportions of CPK released to CPK depleted, variations in this ratio did not appear to influence our results.

Association between extension of infarction and myocardial hemorrhage: Although extension of infarction was not anticipated initially, it became apparent that it was associated with gross myocardial hemorrhage. Results of determinations of hemoglobin in myocardium from animals with myocardial salvage and animals with extension of infarction are shown in Figure 2. Hemoglobin in myocardial tissue from the center of the infarcts and in homogenates prepared from the entire left ventricle was 1,000 and 350 percent greater, respectively, in animals with extension of infarction than in those with myocardial salvage. Thus, extension of infarction after reperfusion was associated with myocardial hemorrhage, which was particularly marked in the central regions of the infarct.

Potential extraneous sources of apparent CPK activity: To exclude spurious contributions to apparent CPK activity from constituents of blood or hemorrhagic myocardium, such as adenylate kinase, ATP and glucose-6-P, we performed assays without creatine phosphate as substrate and measured CPK activity in lysates of red blood cells. Serum CPK isozyme profiles exhibited a "myocardial band"[11] and were comparable in samples from dogs with extension of infarction and those with myocardial salvage, thereby suggesting that the increased CPK in serum was indeed coming from myocardial tissue. Serum samples from both groups of dogs exhibited virtually no CPK activity when substrate was omit-

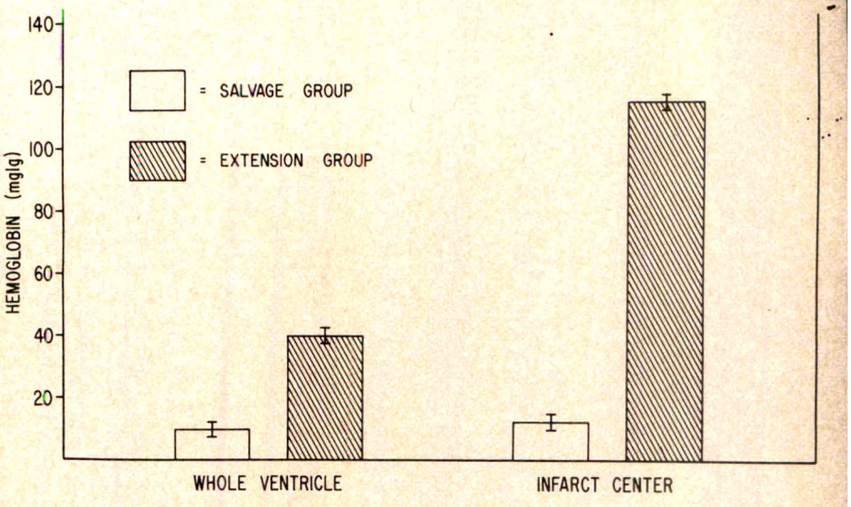

FIGURE 2. Hemoglobin content of homogenates prepared from the whole ventricle **(left)** and from samples obtained from the center of the infarct **(right)** in animals with salvage of myocardium and extension of infarction after reperfusion. Extension of infarction was associated with myocardial hemorrhage manifested by considerable increases in hemoglobin.

ted, excluding appreciable contributions from adenylate kinase, ATP or glucose-6-P. Apparent CPK activity in lysates of red cells was less than 0.2 mIU/mg protein; thus, its contribution to apparent circulating myocardial CPK activity was negligible compared to that of myocardial CPK content (approximately 6 IU/mg protein.[4] Thus, serum CPK activity in samples from animals with myocardial salvage and in animals with extension of infarction did not appear to be influenced spuriously by other constituents from blood or hemorrhagic myocardium potentially capable of influencing the CPK assay.

Discussion

In this study reperfusion of myocardium in conscious dogs 5 hours after coronary occlusion was associated with salvage of myocardial tissue in nine dogs (56 percent) but extension of myocardial injury in the remaining seven dogs (44 percent). The effect of reperfusion on infarct size was assessed by comparing infarct size predicted 5 hours after occlusion, immediately before reperfusion, to infarct size observed during the 24 hour interval after occlusion. The fraction of depleted myocardial CPK released into the circulation was found to be virtually constant (no. = 9).

Factors potentially capable of influencing apparent serum CPK activity such as ATP, adenylate kinase, or glucose-6-P were excluded by assaying samples without substrate in the CPK reaction medium. Red blood cells were excluded as a source of apparent activity by measurement of CPK activity in lysates. In animals with extension of infarction gross hemorrhage was present in the myocardium and documented by measurement of hemoglobin in the tissue. These animals had a 1,000 percent greater increase in hemoglobin in the center of the infarct compared to animals in which reperfusion led to salvage of myocardium. Hemorrhage has been observed after reperfusion of previously occluded cerebral arterial vessels[12] and presumably reflects loss of structural integrity of vessels. Disruption of capillaries and extravasation of blood are detectable by electron microscopy in this setting.

Mechanisms of extension of infarction associated with myocardial hemorrhage: It is not yet clear why only some animals exhibit extension of infarction associated with myocardial hemorrhage whereas others subjected to coronary occlusion for comparable intervals do not. The difference may be related to initial predicted infarct size and to the likelihood that, in general, marginally perfused tissue on the periphery of the infarct is unfavorably influenced by reperfusion whereas jeopardized tissue within more central regions is influenced favorably. Thus, salvage would be more likely to occur in animals with large predicted infarctions since they might have proportionately less tissue in marginally perfused areas than in central zones.

At the conclusion of each experiment the patency of the vessel, the absence of clot and the presence of reflow were confirmed by incising the previously occluded vessel distal to the cuff while the heart continued to beat in situ. However, the possibility that less reflow occurred in the group with myocardial salvage because of spasm or unidentified factors cannot be excluded entirely. Diminished reflow, sufficient to prevent some ischemic tissue from dying but not vigorous enough to lead to extravasation of blood, might have been associated with salvage. In other animals, more complete restoration of reflow, with a resulting intracoronary pressure too great to be tolerated by the anoxic capillary bed, might have led to extension of infarction. An alternate mechanism might involve fewer collateral channels in hearts exhibiting apparent extension of infarction. Regardless of the mechanism, the close association between appreciable myocardial hemorrhage and extension of infarction suggests that hemorrhage in itself is deleterious. It may lead to increased interstitial pressure resulting from accumulation of fluid and potentiated by compression of veins and lymphatic vessels. Retardation of removal of metabolites may contribute to damage. Increased interstitial pressure may inhibit the development of collateral vessels or compress those already present.[14]

Results of this study in concert with those reported previously[1,2] suggest that the time of initia-

tion of reperfusion after coronary arterial occlusion is critical. Salvage of myocardium occurred when reperfusion was initiated 3 hours after occlusion,[1,2] although studies underway in additional animals indicate that some exhibit hemorrhagic infarction. However, the experiments reported here indicate that reperfusion performed 5 hours after occlusion is associated with deleterious effects in a substantial proportion of animals.

Clinical implications: We have previously shown[15] that the extent of depression of ejection fraction in patients with acute myocardial infarction is related to the extent of infarction estimated by analysis of serial serum CPK changes. Results obtained by others[16] indicate that reperfusion 1 to 3 hours after coronary arterial occlusion in cats[16] produces marked improvement in contractility but that little or no functional improvement occurs when reperfusion is delayed for 4 hours. Since improved function may be associated with salvage of myocardium, the results with cats suggest that myocardial salvage can be attained by reperfusion only during a critical interval of 3 to 4 hours.

In view of the availability of saphenous vein bypass graft procedures for patients with acute myocardial infarction, it is essential to determine whether reperfusion is likely to be beneficial under specific circumstances during evolution of infarction. Caution must be exercised in extrapolating our results to patients. The anatomy of the coronary arteries and the nature of collateral vessels differ considerably from species to species. Experimental coronary occlusion is not necessarily comparable to spontaneous clinical myocardial infarction,[17] in which diminished flow without complete occlusion frequently occurs. Yet, early experience with valvular surgery suggests that our findings may be relevant to patients. Hemorrhagic necrosis has been observed after valvular replacement particularly in patients who died in the early postoperative period.[18,19] Its incidence appears to be related to the duration of cardiac arrest and of myocardial hypoxia. In patients with coronary artery disease who underwent valve replacement hemorrhage occurred only when intermittent reflow was permitted during induced cardiac arrest. Furthermore, hemorrhage was associated with capillary damage detectable by electron microscopy.[20] Hypertrophied myocardium may be particularly sensitive to ischemia and prone to hemorrhagic 'necrosis.[18] Thus, severity of hemorrhagic necrosis may depend not only on the duration of myocardial hypoxia but also on the extent of hypertrophy antedating interruption of coronary flow. The results of our experimental investigation indicate that the effects of reperfusion during evolving myocardial infarction are sometimes deleterious. Further elucidation is needed of the effects of revascularization on functional and structural integrity of the myocardium in patients with coronary artery disease, particularly during impending or evolving myocardial infarction.

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Physiologic Basis for Assessing Critical Coronary Stenosis

Instantaneous Flow Response and Regional Distribution During Coronary Hyperemia as Measures of Coronary Flow Reserve

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Quantitative hemodynamic assessment of coronary stenosis has not been previously reported. Resting coronary blood flow and its regional distribution are insensitive indexes for determining critical stenosis, but flow response to a hyperemic stimulus quantifies restrictions on maximal flow due to coronary arterial lesions. Coronary flow responses to temporary occlusion and to selective main coronary arterial injection of sodium diatrizoate (Hypaque-M 75 percent) were studied in 12 consecutive dogs with a surgically implanted electromagnetic flowmeter and separate micrometer constrictor on the left circumflex coronary artery. Selective Hypaque injection adequate for coronary cineangiography increased coronary flow to four times the resting base-line value, peaking at 6 seconds and lasting 3 minutes, a response equivalent to hyperemia after 10 seconds of circumflex arterial occlusion. With progressive micrometer constriction, resting flow measurements did not decrease until there was 85 percent stenosis. Hyperemia after intracoronary injection of Hypaque decreased when there was 30 to 45 percent stenosis and disappeared when there was 88 to 93 percent stenosis. Myocardial images obtained by gamma camera after left atrial injection of ^{131}iodine-macroaggregated albumin demonstrated uniform regional distribution of resting flow in spite of severe constriction. However, 6 seconds after selective Hypaque injection, left atrial injection of ^{99m}technetium macroaggregates demonstrated distinct perfusion abnormalities in the region of circumflex stenosis. Thus, flow distribution with a severe lesion was normal at rest but showed marked differences due to restricted circumflex versus normal anterior descending hyperemic response after injection of Hypaque. Flow response and regional distribution during coronary hyperemia caused by Hypaque are quantitative measures for physiologically assessing critical coronary stenosis and flow reserve with potential applicability to patients.

Previous efforts at quantitative evaluation of coronary arterial lesions in terms of altered coronary blood flow have been largely unrewarding, in part because of limitations in present techniques for measuring coronary flow in man.[1,2] However, an equally likely explanation may be that resting coronary blood flow and its distribution are unaffected by relatively severe constrictive lesions. Studies on peripheral arteries have demonstrated that a stenosis that markedly impairs flow at high levels of flow velocity has little effect at resting or low flow velocity levels.[3,4] It is therefore essential to evaluate coronary arterial lesions in terms of altered maximal, rather than resting, coronary blood flow. Despite this need, quantitative data on the effects of progressive coronary arterial constriction on maximal flow have not been previously reported. This study describes the physiologic basis of an approach for assessing the hemodynamic effects of coronary lesions on maximal blood flow or coronary flow re-

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serve independent of arteriographic interpretation. Our approach was used initially to determine critical coronary stenosis in dogs and to establish experimentally the relation between severity of constriction, resting and maximal coronary blood flow and regional flow distribution. Critical coronary stenosis is defined here as a constriction sufficient to prevent an increase in flow over resting values in response to increased myocardial oxygen demands; as subsequently shown, this constriction also corresponds to the point at which resting coronary flow values start to decrease. With appropriate instrumentation our approach appears to be applicable to patients during cardiac catheterization.

Methods

Twelve consecutive 17 to 40 kg black Labrador or German shepherd dogs were prepared as follows: Anesthesia was induced with sodium pentobarbital (Diabutal®) 1 hour after subcutaneous administration of 45 mg of morphine sulfate. Respirations were controlled with a Harvard ventilatory pump through a cuffed endotracheal tube. Respiratory volumes were monitered continuously with a Draeger volumeter and blood gases were maintained normal by volume adjustment or by the addition of oxygen if necessary. The left circumflex coronary artery was isolated through a left thoracotomy, the arterial diameter was measured with calipers, and an appropriately sized, perivascular electromagnetic flowmeter transducer (Zepeda) was implanted. An occluder of the snare type attached to a machinist's micrometer was placed distal to the transducer before arterial branching. The snare could be closed by small, precise amounts according to the 0.01 mm micrometer scale. A 36 cm no. 9F catheter was inserted into the right carotid artery and advanced into the ascending aorta for recording pressure and a no. 4F catheter was inserted into the left atrium for subsequent injection of radionuclides.

A standard no. 7.5F, Positrol, Sones coronary arteriographic catheter was inserted through the left carotid artery and positioned under fluoroscopy at the orifice of the main left coronary artery so that both the circumflex and anterior descending branches could be simultaneously visualized by injection of sodium diatrizoate (Hypaque®-M 75 percent, Winthrop Laboratories). This catheter was easily positioned in the dog, usually in only a few minutes, and remained stable in position for several hours. The catheter did not interfere with coronary flow, even at high flow rates, as indicated by sudden withdrawal of it during peak hyperemia (see later).

Coronary flow was recorded with a Zepeda square wave, electromagnetic flowmeter operating at 400 Hz and perivascular flow transducers calibrated in vivo by beaker and stopwatch. Central aortic pressure was measured with a Kulite solid state PSL 126-6 or Statham P23 Db pressure transducer. Data were recorded on a 12 channel, Electronics for Medicine physiologic recorder. Coronary cineangiograms were made on 16 mm Kodak Shellburst film with a 9 inch Kelekat fluoroscopy-cine unit using a grid with 80 lines/inch.

Experimental procedure: All dogs were heparinized. Occlusive zero base line for the electromagnetic flowmeter was established at the beginning of each experiment and corresponded to occlusive zero after each experiment. Coronary hyperemic response after 10 seconds of complete occlusion of the left circumflex artery produced by gently clamping the artery was recorded twice consecutively. The Sones catheter was positioned at the coronary orifice and the hyperemia after 10 seconds of occlusion was again recorded twice consecutively to demonstrate that the catheter did not interfere with flow during hyperemia. A base-line coronary cineangiogram was obtained using 2 to 4 cc of Hypaque-M 75 percent to determine the amount required for adequate visualization of the left anterior descending and circumflex arteries. The same dose of Hypaque was subsequently used throughout an experiment.

As detailed under Results, intracoronary administration of Hypaque caused marked coronary hyperemia of three to seven times resting base-line flow values, a response equivalent to the hyperemia occurring after 10 seconds of complete occlusion. Because of these effects, contrast medium was utilized as a convenient means of recurrently stimulating coronary vasodilatation and increased flow. The hyperemic response to the selected Hypaque dose was recorded twice consecutively after the initial cineangiogram. The micrometer constrictor was then tightened around the artery until it fit snugly without causing a constriction noted on visual inspection or by coronary angiography. The micrometer reading at this point was recorded as a "no lesion" base line. From this base line the micrometer constrictor was tightened in steps progressing from no lesion to complete occlusion in 11 to 19 increments. At each step, the base-line resting coronary flow and the hyperemic response to Hypaque were recorded and a cineangiogram was obtained. Total excursion of the micrometer was determined from the base-line micrometer reading at no lesion and the reading at 100 percent occlusion. Percent lesion by diameter was then calculated for each intervening micrometer setting by the following equation:

$$\%\ \text{lesion} = 100\,[(\text{micrometer reading at no lesion} - \text{reading at each step})/\text{total micrometer excursion}]$$

Thus, values for resting and maximal coronary blood flow were obtained for a series of progressively severe coronary lesions up to complete occlusion.

Regional flow distribution was evaluated during rest and hyperemia by double radionuclide studies at a point during progressive constriction when the hyperemic response was blunted but the resting flow rate was still normal. The purpose was to determine whether moderately severe constriction that did not alter normal resting flow caused abnormalities in regional flow distribution at rest or at increased flow rates. At this point during constriction, 2 mCi of ^{131}iodine-macroaggregated albumin was injected through the left atrial catheter. Without further constriction, intracoronary Hypaque was injected through the Sones catheter and 6 seconds later 7 mCi of ^{99m}technetium-macroaggregated albumin was injected into the left atrium. Myocardial tissue supplied by the left anterior descending coronary artery could respond normally with a marked increase in perfusion during Hypaque-induced hyperemia. However, myocardial tissue supplied by the constricted left circumflex artery could not increase perfusion normally in response to the hyperemic stimulus. Thus, regional distribution of coronary flow could be ascertained during the resting base-line period, when all areas of myocardium were likely to be equally perfused, in spite of 80 to 85 percent stenosis of the left circumflex artery and during maximal hyperemia when differences between normally and abnormally perfused areas were maximal.

TABLE I

Effect of Intracoronary Hypaque Injection and 10 Seconds of Occlusion on Mean and Peak Phasic Left Circumflex Arterial Flow

Experiment No.	Body Weight (kg)	LC OD (mm)	Hypaque (cc/kg)	Control Mean LC Flow (cc/min)	Increase After Hypaque (× control)	Increase After Occlusion (× control)	Control Peak Phasic LC Flow (cc/min)	Increase After Hypaque (× control)
1	17	3.0	0.12	29	3.5	3.4	47	3.0
2	25	3.4	0.12	83	3.6	3.1	114	3.5
3	30	3.5	0.13	70	3.6	3.9	100	3.4
4	23	3.0	0.09	34	3.9	3.8	57	3.3
5	23	3.7	0.13	32	3.5	4.1	50	3.1
6	31	3.0	0.13	27	5.0	5.0	42	4.4
7	23	3.7	0.13	51	2.7	4.0	74	2.5
8	38	3.5	0.11	41	5.4	4.4	69	4.6
9	26	3.0	0.12	40	4.7	6.8	68	4.3
10	40	3.8	0.10	48	3.2	4.5	78	2.9
11	23	3.0	0.17	64	3.0	4.1	111	2.6
12	27	3.6	0.15	61	4.8	4.2	99	4.1
Mean ± SD	27 ± 7	3.3 ± 0.3	0.12 ± 0.02	48 ± 18	3.9 ± 0.9	4.3 ± 0.9	76 ± 24	3.5 ± 0.7

LC = left circumflex; OD = outside diameter; SD = 1 standard deviation.

At the end of each experiment the micrometer constrictor was released and the responsiveness of the coronary bed was tested twice consecutively by recording hyperemia after 10 seconds of occlusion. The animal was sacrificed, the heart removed and the left ventricle dissected from the rest of the heart. The ventricle was opened by cutting from base to apex along the left anterior descending coronary artery. The resulting specimen was placed flat with the left ventricular endocardium down for heart imaging (see upper right photograph, Fig. 4). Myocardial tissue supplied by the circumflex coronary artery was in the center of the specimen surrounded by myocardial tissue in the area perfused by the left anterior descending artery.

In this initial study, heart scans were made in postmortem specimens to document regional flow distribution as accurately as possible without the compromising problems of counting geometry in the intact animal. Images of the left ventricle were obtained on a Nuclear-Chicago HP gamma camera, using a pin-hole collimator; 100,000–400,000 count pictures were obtained of both ^{131}iodine and ^{99m}technetium distribution using a pulse-height analyzer with a 20 percent window. Small region-of-interest scans of equal size were then placed over specific areas of ventricular myocardium supplied by the left anterior descending or left circumflex coronary arteries. Counts from each region-of-interest scan were collected for 2 minutes and expressed as percent of total counts of the entire ventricle. ^{99m}technetium counts were corrected for ^{131}iodine cross-talk by counting a ^{131}iodine standard of the same geometric shape as the left ventricular sample.

Data analysis: For each dog, all flow measurements were divided by control or base-line resting coronary flow values recorded before each 10 second occlusion at the beginning of the experiment. The resulting ratios permitted comparisons between dogs of the changes in resting flow and hyperemic responses at each progressive step in coronary arterial constriction. For example, a flow ratio of 3.5 indicates that hyperemic flow was 3.5 times resting base-line flow values. A ratio of 1.0 indicates that there was no change from resting base-line values and a ratio of less than 1 indicates that flow values decreased below resting control values recorded at the beginning of each experiment. With a PDP 8 computer, flow ratios for each dog were plotted against percent constriction by multivariate regression analysis using the least squares fit to a power series to obtain the best fit curve and polynomial equations relating flow to percent lesion.[5] Composite curves and equations for all data combined from the 12 dogs were also obtained by multivariate regression analysis.

Results

Coronary flow responses: Table I shows body weight, diameter of the left circumflex artery, the standard visualizing dose of Hypaque-M 75 percent per kilogram body weight, resting control circumflex flow values and flow responses to Hypaque and to 10 second occlusion. Values for the hyperemic responses are expressed as ratios to base-line flow as described under Methods. For example, in the absence of constriction, mean circumflex arterial flow was 48 ± 18 (mean ± 1 standard deviation) cc/min and increased 3.9 ± 0.9 times after Hypaque injection. Control peak phasic (diastolic) circumflex flow was 76 ± 24 cc/min and increased 3.5 ± 0.9 times after injection of Hypaque. The response peaked 6 ± 1 seconds after injection, after all contrast had been washed from the coronary bed, and lasted 1 to 4 minutes. These responses to Hypaque are equivalent to the reactive hyperemia occurring after 10 seconds of complete occlusion of the left circumflex artery (Table I). In some dogs flow increase after Hypaque was greater than after 10 seconds of occlusion, probably because of biologic variation in the relative effectiveness of the arbitrary dose of Hypaque and arbitrary duration of temporary occlusion as stimuli for vasodilation. Mean base-line heart rate and systolic and diastolic aortic pressures were 143 ± 21 beats/min, 151 ± 22 mm Hg and 121 ± 18 mm Hg, respectively,

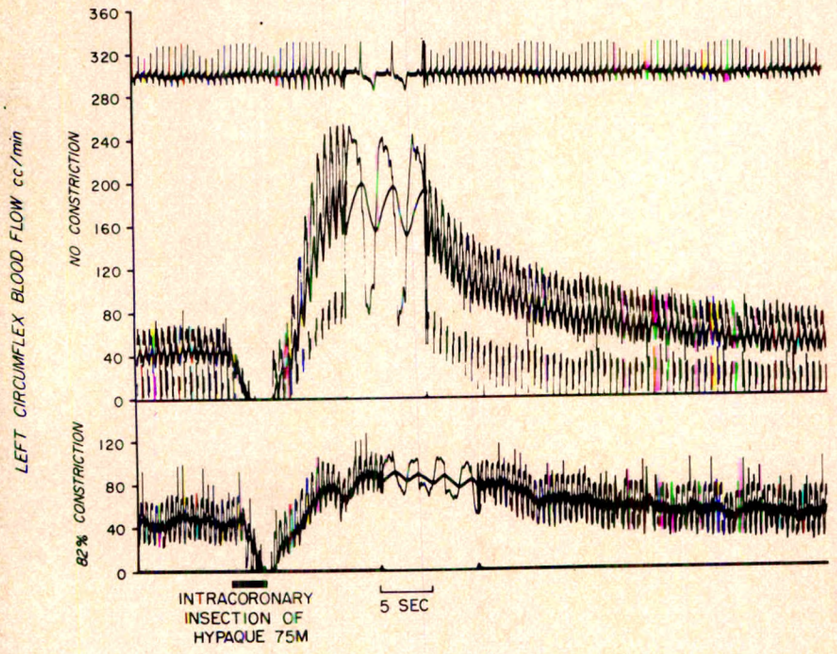

FIGURE 1. Hyperemic flow response in the left circumflex artery after intracoronary injection of Hypaque with no constriction **(upper tracing)** and with 82 percent constriction by diameter **(lower tracing).** The impairment of hyperemia **(lower tracing)** affects mean and peak phasic (diastolic) flow. **Heavy lines** indicate mean flow. Paper speeds are 5 and 25 mm/sec.

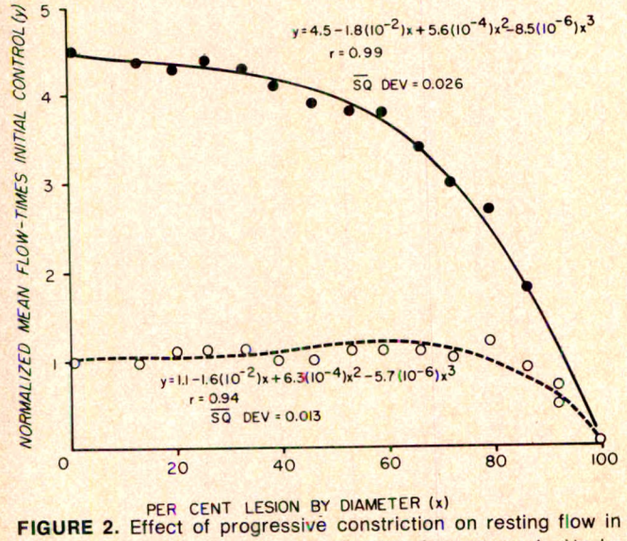

FIGURE 2. Effect of progressive constriction on resting flow in the left circumflex artery (––) and hyperemic response (—) to intracoronary injection of Hypaque in a single dog. Percent constriction by diameter is shown on the **horizontal** axis. Resting and mean hyperemic flow after Hypaque injection, expressed as the ratio of measured to control base-line flow values, is shown on the **vertical** axis. SQ DEV = mean square of deviations.

with no significant mean changes after intracoronary injection of contrast medium.

Hyperemia after injection of Hypaque is illustrated in Figure 1 by a recording of flow in the left circumflex artery. The upper tracing shows no constriction and a four-fold increase in flow in response to the injection. The lower tracing, obtained during 82 percent constriction of the left circumflex artery, shows a blunted hyperemic response; both mean and peak phasic (diastolic) flow responses are markedly reduced. Injection of saline solution did not affect coronary flow.

Figure 2 demonstrates the results of a typical single experiment. With progressive constriction of the left circumflex artery, the normal hyperemic response to Hypaque became blunted when there was 35 percent narrowing and diminished markedly before resting flow was affected. Every dog demonstrated results similar to those of Figure 2 with little scatter of data from the best fit curve, as indicated by correlation coefficients ranging from 0.98 to 0.99 and mean square deviations from 0.115 to 0.003. Figure 3 shows the relation between percent constriction, resting mean flow ratio and mean flow ratio after injection of Hypaque for all dogs. Resting mean flow was not affected until 85 percent constriction occurred, whereas hyperemic response was blunted when there was 45 percent narrowing, decreased precipitously before resting flow was affected, and was gone when narrowing was 93 percent.

Peak phasic or diastolic flow ratios correlated with percent constriction for all dogs together (r = 0.91; mean square deviation = 0.214); the plot and equation are similar to those shown in Figure 3. However, peak phasic flow ratios were affected to a greater extent than mean flow ratios for a given degree of narrowing. Although resting peak phasic flow ratio was unaffected until there was 85 percent stenosis, hyperemic peak phasic response to Hypaque began to fall with 30 percent stenosis and was gone with 88 percent stenosis.

Myocardial flow distribution: An example of myocardial flow distribution before and after injection of contrast medium is presented in Figure 4. Be-

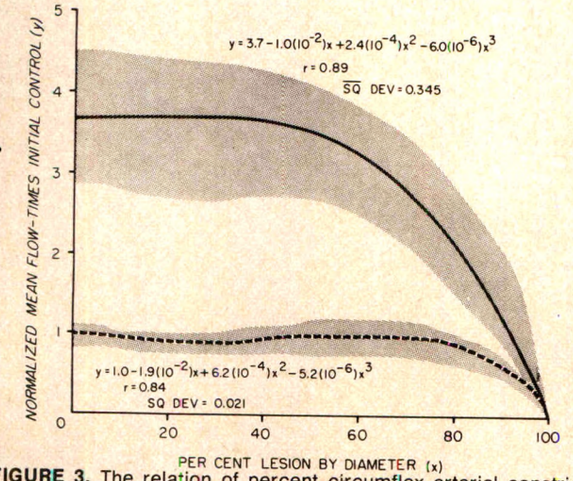

FIGURE 3. The relation of percent circumflex arterial constriction by diameter to resting mean flow(--)and hyperemic response(—)after intracoronary injection of Hypaque in 12 consecutive dogs. Flows are expressed as ratios to control resting mean values at the beginning of each experiment. The **shaded area** indicates the limits of the relation plotted for individual dogs. r = correlation coefficient. $\overline{SQ}$ DEV = mean square of deviations.

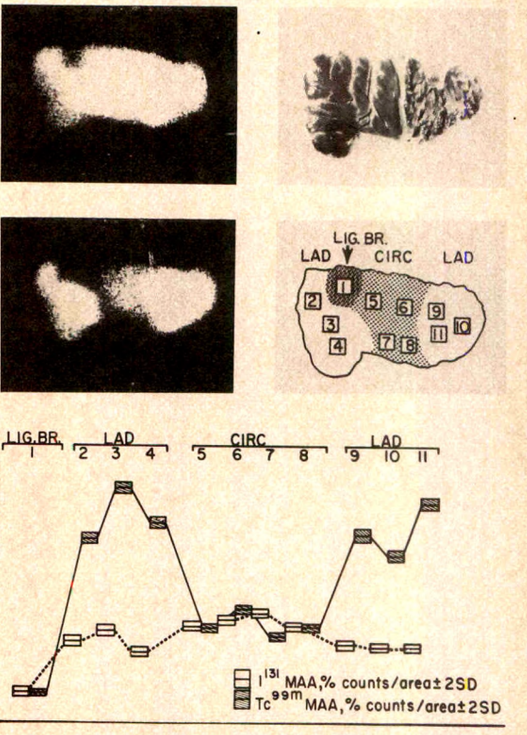

FIGURE 4. Left ventricular regional flow distribution in a dog before and after hyperemic stimulus during 80 percent constriction of the left circumflex artery (CIRC). The dissected, opened left ventricle is positioned endocardium down for postmortem heart scanning **(upper right).** The areas perfused by the circumflex artery are in the center of the specimen surrounded by myocardium supplied by the left anterior descending artery (LAD). The ^{131}iodine image **(upper left)** shows normal resting flow distribution in spite of 80 percent constriction of the left circumflex artery. After intracoronary injection of Hypaque, a ^{99m}technetium image **(lower left)** shows abnormal regional perfusion due to a normal hyperemic response in the anterior descending artery but lack of response in the constricted circumflex vessel. The location of small, equal-sized, region-of-interest scans are indicated by the drawing on the lower right corresponding to the photographed specimen above. Counts for each region-of-interest scan, expressed as percent of total ventricular counts (percent of total ventricular flow), are plotted on the **vertical axis** of the graph with its corresponding location on the ventricle indicated by number on the **horizontal axis.** The graph is a quantitative, rather than visual, demonstration of regional coronary flow distribution. Lig.Br. = a very small coronary branch ligated during transducer implantation.

fore injection, the distribution of myocardial flow was uniform in spite of 80 percent constriction of the left circumflex artery. After injection, there was a marked increase in perfusion of myocardium supplied by the normal left anterior descending coronary artery. However, myocardium within areas perfused by the left circumflex artery failed to demonstrate comparable hyperemia due to the constriction. Thus, flow distribution with an 80 percent lesion was normal at rest but showed marked abnormalities after injection of Hypaque because of the inability of flow to increase in the circumflex artery in response to hyperemic stimulus. The heart image was quantitatively analyzed by making several small, equal-sized region-of-interest scans distributed over myocardium supplied by the left anterior descending and circumflex arteries. The location and approximate size of the areas of interest for this example are demonstrated in the drawing of Figure 4. The number of counts recorded from each area of myocardium was divided by the total number of counts from the entire left ventricle and represents the percent of total left ventricular flow to that area. The graph in Figure 4 shows the percentage of left ventricular flow for the various areas of the myocardium at rest and after hyperemic stimulus. This example quantitatively demonstrates that with 80 percent stenosis of the left circumflex artery, resting flow to areas perfused by the circumflex and anterior descending arteries was relatively equal. After injection of Hypaque, the percent flow to each area perfused by the left anterior descending artery increased markedly but changed relatively little in areas perfused by the left circumflex artery. This relative maldistribution of flow during hyperemia caused an abnormal scan pattern after injection of Hypaque.

The visual and quantitative differences illustrated in Figure 4 may also be expressed as the ratio of counts over myocardium supplied by the anterior descending artery to counts over the myocardium supplied by the circumflex artery before and after the hyperemic stimulus. These ratios were averaged for all dogs (Fig 5). The mean data in Figure 5 were obtained with a mean left circumflex constriction of 85 percent by diameter. During resting flow measurements, before injection of Hypaque, the maximal ratio between peak counts for the left anterior descending artery and mean counts for the circumflex artery was 1.0 ± 0.2, indicating uniform flow distribution. However, after injection of Hypaque, this

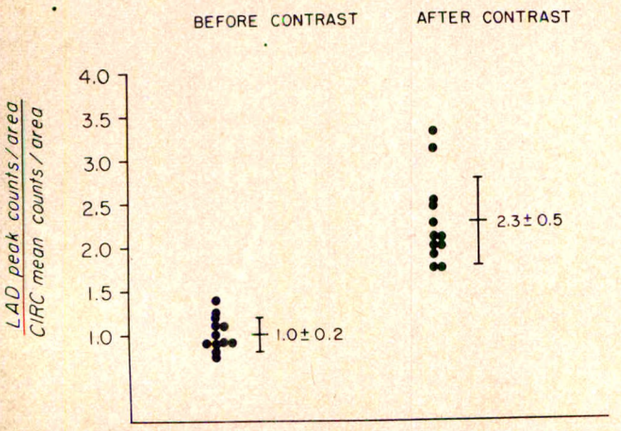

FIGURE 5. Left ventricular regional flow distribution in 12 consecutive dogs before and after hyperemic stimulus in the presence of an average 85 percent constriction of the left circumflex artery. The vertical axis shows the ratio of counts from myocardium supplied by the anterior descending artery (LAD counts) to counts from myocardium supplied by the constricted circumflex artery (CIRC counts). The ratios are significantly different ($P < 0.001$), thus demonstrating normal flow distribution at rest but markedly abnormal distribution during hyperemia.

ratio increased to 2.3 ± 0.5 ($P < 0.001$), indicating markedly abnormal flow distribution. Since the borders of myocardium supplied by the left anterior descending artery are not sharply delineated from those supplied by the circumflex artery, similar ratios were also calculated using mean counts from all small areas of interest taken over the areas perfused by the left anterior descending artery in each dog. Average ratios between mean counts for the left anterior descending and circumflex arteries were 0.9 ± 0.2 before injection of Hypaque and 1.8 ± 0.3 after injection ($P < 0.001$), again demonstrating the differences in regional perfusion during hyperemia but not with resting coronary flow levels.

Discussion

Critical coronary stenosis and the quantitative effects of progressive coronary arterial constriction on maximal coronary flow or coronary flow reserve have not been previously described. Resting coronary flow and its regional distribution are little affected by relatively severe stenosis and are therefore insensitive measures for evaluating coronary disease. Our data demonstrate that resting coronary flow is not altered until a constriction of at least 85 percent by diameter is present, whereas maximal coronary flow is affected by constriction as small as 30 percent. The capacity to increase coronary flow significantly in response to additional oxygen demands is abolished when there is 88 to 93 percent constriction, just after resting flow begins to diminish and this period is defined here as critical coronary stenosis. Thus, although the coronary arteriogram does provide anatomic definition of coronary lesions, it offers little insight into their hemodynamic consequences short of total or near total occlusion. This limitation is a particular problem in the presence of multiple lesions with cumulative effects on maximal coronary flow. With the advent of saphenous vein bypass surgery, hemodynamic assessment of coronary arterial lesions is of considerable practical importance.

Flow response to hyperemic stimulus as measure of effects of coronary constriction: An effective approach to physiologic evaluation of coronary lesions in man depends on solution of three related problems: (1) a method for following rapid changes in coronary flow and flow distribution; (2) a safe and convenient stimulus for increasing coronary blood flow, and (3) a background of basic experimental data relating severity of a lesion to resting and maximal blood flow or coronary flow reserve. This report describes an approach to these problems. The data presented indicate that the flow response to a hyperemic stimulus is in itself an excellent measure of the effects of coronary constriction. Flow responses have been presented in comparison to the more conventional means of describing lesions by percent of diameter constriction in order to demonstrate this approach. However, it should be emphasized that flow response to hyperemic stimulus provides independent, complementary information on the hemodynamic significance of angiographically demonstrated lesions.

Temporary occlusion of major coronary arteries is a potent stimulus for hyperemia, probably because of accumulation of vasodilator substances during the period of occlusion.[6] In chronically prepared intact dogs, occlusions of 5 to 7 seconds' duration are sufficient to elicit maximal increases in coronary stroke flow of three to seven times resting base-line value, and the absolute value is constant in an animal for a given period of occlusion.[6] It has also been noted incidentally during studies of collateral vessel development that reactive hyperemia diminishes during gradual occlusion by ameroid constriction, before resting flow rates are affected.[7] However, in these experiments the degree of constriction was not measured. Although described more completely in dogs, hyperemia also occurs after occlusion in man, as documented during saphenous vein bypass surgery.[8,9]

Temporary coronary occlusion as a stimulus to increased blood flow is unacceptable for diagnostic purposes in man. A number of other stimuli have been used experimentally. Physical exercise in trained dogs increases coronary flow two to five times above resting values.[10-12] Increasing heart rate from 60 to 260 beats/min by electrical pacing increases coronary flow only two times over control levels in unanesthetized intact dogs.[13] Intravenous administration of Persantin® may increase blood flow in dogs four-fold.[11] Administration of pharmacologic agents, such as norepinephrine,[14] nitroglycerin,[15] adenosine triphosphate and adenosine diphosphate,[16] also increases coronary flow but to a lesser extent than temporary occlusion. None of these techniques appear to provide a convenient, safe or effective method of stimulating brief hyperemia in man.

Intracoronary contrast agents are known to cause coronary vasodilatation and increased blood flow in both animals[17,18] and man[19] although the mechanisms are unknown. However, the timing, degree and duration of this response have not been adequately described or utilized previously. Our results indicate that Hypaque-M 75 percent in doses adequate for cineangiography causes brief, marked hyperemic responses that are three to seven times base-line values and equivalent to the reactive hyperemia observed after 10 seconds of complete occlusion. In man, coronary flow has been reported to increase only 15 to 35 percent after injection of contrast medium.[19] However, in that study flow was measured by the ^{133}xenon technique, which is quantitatively inaccurate in the presence of the heterogenous flow distribution found in coronary disease, particularly at increased flow rates.[22-24] In addition, use of this method assumes that coronary flow is constant during the 1 to 3 minute period of xenon washout.[25] There is no evidence to support this assumption and our flowmeter data indicate the contrary, that is, that coronary flow is not constant during the minutes after injection of Hypaque. Differences in species may also explain some of these quantitative differences in responses to Hypaque. Since Hypaque is used clinically in man for coronary angiography, it is a satisfactory stimulus for hyperemia in assessing the effects of lesions at increased flow rates.

Quantification of coronary flow reserve: The concept of coronary flow reserve is essential to the evaluation of coronary disease, but heretofore no approach has been reported for quantifying it. Coronary reserve relates to the ability of coronary vessels to increase blood flow in response to oxygen demands or as compensation for decreased oxygen carrying capacity of blood, or both. It is equivalent to the maximal coronary blood flow after oxygen deficit, that is, complete occlusion. For a given stimulus, this maximal or ceiling flow rate is constant for a given animal and ranges from three to seven times resting base-line flow values. Increases in base-line flow that "use up" some of this reserve result in less potential increase available to meet additional acute oxygen demands. For example, in this study an abnormally low level of arterial PO_2 usually caused an increase in base-line coronary flow but did not affect the absolute value of peak hyperemia. As a result, any relative increase compared to base-line flow values was reduced and remaining coronary reserve thereby diminished. For this reason, arterial PO_2 was carefully maintained within normal limits. Clinical situations corresponding to this experimental observation are found in disease states in which base-line coronary flow levels are elevated, such as anemia, thyrotoxicosis, pressure-volume overload or altitude hypoxia. The observed decrease in exercise tolerance due to cigarette smoking has been ascribed to increased time-tension index for a given level of exercise,[20] that is, increased oxygen demands, and to abnormally high arterial carbon monoxide levels, that is, decreased oxygen-carrying capacity. Thus, the deleterious effects of smoking on exercise tolerance may be viewed in terms of decreased or "used up" coronary flow reserve.

Coronary flow reserve distribution: An equally important concept not previously described is that of distribution of coronary flow reserve. Even if total coronary flow reserve were relatively intact in the face of localized disease, the distribution of blood to small regions of myocardium may become markedly abnormal during hyperemia. Our data indicate that resting flow distribution may be normal in the face of severe constriction of a coronary branch but that regional distribution becomes grossly abnormal after a hyperemic stimulus. Irregular or patchy myocardial regional perfusion which occurs in coronary disease is thus greatly exaggerated with stimuli for increased coronary flow.

Clinical applications: A physiologic approach and a hyperemic stimulus appropriate for evaluating coronary constriction have been described in this report. The application of this approach to man requires a method for following rapid changes in coronary flow and of assessing its regional distribution. Although coronary flow was measured with a surgically implanted electromagnetic flowmeter, we have also monitored changes in coronary flow velocity during canine coronary angiography using a Sones catheter with an ultrasonic, velocity sensing tip. Coronary flow velocity has been recorded in man with a similar instrument.[21] Values for flow velocity can be converted to absolute coronary flow values only if the diameter of the vessel and the angle between the flow stream and beam of ultrasound are known, two factors that have been drawbacks to its clinical use. However, since the ratio of hyperemic to resting flow velocity is equal to the ratio of hyperemic to resting absolute flow, it is not necessary to know vessel size or catheter angle to measure coronary flow reserve. Thus, our approach appears to be technically feasible. However, presently available ultrasonic coronary catheters for use in man do not have a lumen and therefore do not permit injection of contrast medium. A catheter that can be used to obtain cineangiograms and simultaneous velocity recordings requires development for use in patients. Videodensitometry also provides a particularly promising approach for measuring relative and absolute flow changes in each coronary artery. Flow distribution may be evaluated in man with the gamma camera. Although problems of counting geometry and spatial resolution have to be solved, our approach maximizes differences in regional perfusion and therefore should provide diagnostic information for physiologic assessment of the effects of coronary lesions independent of arteriographic interpretation.

Clinical implications: The usefulness of this approach in the clinical setting is speculative at present. Since the relation of flow and stenosis reflects fundamental physical principles, it is reasonable to extrapolate some of the results to man. Thus, a short

lesion of 45 to 50 percent by diameter probably does not impair coronary flow reserve in man but more severe lesions cause a progressive decrease. Unfortunately, prediction of flow reserve from angiographic appearance of a coronary lesion is difficult. Marked impairment of coronary flow reserve occurs with progressive stenosis of 65 to 95 percent by caliper determination, but with lesions of this degree angiography is not sufficiently accurate for measuring small luminal changes having major hemodynamic consequences; this limitation is compounded by multiple or long areas of stenosis. A more physiologic approach might be utilized if responses to Hypaque were established for normal and diseased human coronary arteries by clinical studies using a velocity sensing catheter, videodensitometry or gamma camera. Possibly a hyperemic/base-line flow ratio of less than 1.5 would be an indication for surgery. However, further investigation is essential before these concepts are of practical value in managing patients.

Acknowledgment

We are indebted to Cynthia Calvert for technical assistance in these studies.

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Cardiac Specialized Tissue in Hearts with an Apparently Single Ventricular Chamber (Double Inlet Left Ventricle)

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The morphologic and histologic findings in 14 univentricular hearts are described. All hearts had a single ventricle with a main chamber receiving both atrioventricular orifices and giving rise to the posterior great vessel. The anterior great vessel arose from a smaller outlet chamber.

The main finding was a grossly abnormal situation of the cardiac specialized tissue. Thus, in all 14 hearts the atrioventricular node was a small hypoplastic structure in the interatrial septum. Connection between the atria and ventricles was made by way of an anterior node situated at the junction of the right atrial appendage with the anterior interatrial septum. From this node an atrioventricular bundle descended in the outflow tract of the posterior vessel and lay on the right margin of the foramen between the main and outlet chambers. The bundle was found in this position in both dextro- and levo-bulboventricular loops. The bundle bifurcated astride the septum between the chambers, and a typical left bundle branch passed into the main chamber. Right bundle branch tissue was always present in the outlet chamber. In two hearts with complete heart block neither node made contact with ventricular myocardium, but specialized tissue was present in the ventricular subendocardium.

Because these findings have significance for surgical treatment, it is important to distinguish such hearts from "common" ventricles in which the specialized tissue is reported to lie in the posterior position. The mode of development of the abnormal tissue is discussed, with particular reference to the presence of anterior nodal tissue in normal human development. Finally, it is concluded that either of two concepts could account for the morphogenesis of the anomaly and that further studies are necessary to determine the correct hypothesis.

Hearts with a single or apparently single ventricular chamber have been extensively investigated for more than a century, as documented in a review by Van Praagh et al.[1] in 1964. Two later studies have shown that disagreement exists on several important features of such hearts.[2,3] First, there are fundamental differences of opinion on nomenclature. Thus, Lev et al.[2] use the adjectives "single" and "common" to describe two subgroups of the malformation. Van Praagh et al.,[1] disagreeing with this usage on semantic grounds, use the adjectives interchangeably. The term "double inlet left ventricle" [3] is criticized by Lev's group, who believe the main chamber of such hearts is composed of the sinuses of both ventricular chambers. An extension of this latter point produces the second source of controversy. Thus, the tissue between the chambers in the "single" ventricle (terminology of Lev et al.) is considered to be either bulbar in origin[2] or to represent the true interventricular septum.[1]

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TABLE I

Pathologic and Histologic Features of 14 Hearts Studied

Case no.	Morphologic Features						Histologic Findings					
							Posterior Node		Anterior Node			
	Atrial Chambers	BVL	TGV	A–V Valves	Tissue Arising from Outlet Chamber	Associated Anomalies	Features	Contact with Ventricles	Features	Contact with Ventricles	A–V Bundle	Conduction Tissue in Outlet Chamber
1	Solitus	D	D	Hypoplasia of TV	Absent	None	Specimen mutilated	Specimen mutilated	Poorly formed	Yes	Specimen mutilated	Present
2	Solitus	D	D	Normal	Absent	None	Well formed	No	Well formed	Yes	Right rim of BVF	Present
3	Solitus	D	D	Normal	Absent	None	Well formed	No	Well formed	Yes	Right rim of BVF	Present
4	Solitus	D	D	Normal	Absent	Absent BVF; PFO; PDA	Well formed	No	Well formed	Yes	Present in septum	Present
5	Solitus	D	D	Mitral stenosis	Valve tissue from outlet chamber	Coarctation; PFO; PDA	Well formed	No	Well formed	Yes	Right rim of BVF	Present
6	Solitus	D	D	Normal	Valve tissue from outlet chamber	PFO; PDA	Well formed	No	Not identified	?	Right rim of BVF	Present
7	Solitus	D	D	Normal	Valve tissue from outlet chamber	None	Well formed	No	Not identified	...	Not identified	Present
8	Solitus	L	L	Normal	Valve tissue from outlet chamber	PFO; PDA	Not identified	...	Poorly formed	Yes	Right rim of BVF	Present
9	Solitus	L	L	Normal	Pap. muscle on rim of BVF	None	Poorly formed	No	Identified	Yes	Right rim of BVF	Present
10	Solitus	L	L	Normal	Absent	Pulmonary stenosis	Well formed	No	Well formed	Yes	Right rim of BVF	Present
11	Solitus	L	L	Normal	Absent	None	Poorly formed	No	Hemorrhage in septum	Traumatic heart block	Hemorrhagic	Present
12	Solitus	L	L	Parachute deformity of left A–V valve	Absent	None	Well formed	No	Well formed	No	Right rim to left rim of BVF	Present
13	Solitus	L	L	A–V canal	Absent	Poorly formed LA septum	Ring muscle R side of canal	No	Ring muscle R side of canal	No	Not identified	Present
14	Solitus	L	L	Left–A–V valve straddles BVF	Straddling	None	Poorly formed	No	Not identified	...	Right rim of BVF	Present

A–V = atrioventricular; BVF = bicuspid valve foramen; BVL = bulboventricular loop; D = dextro-; L = levo-; LA = left atrial; Pap .= papillary; PDA = patent ductus arteriosus; PFO = patent foramen ovale; R = right; TGV = transposition of great vessels; TV = tricuspid valve.

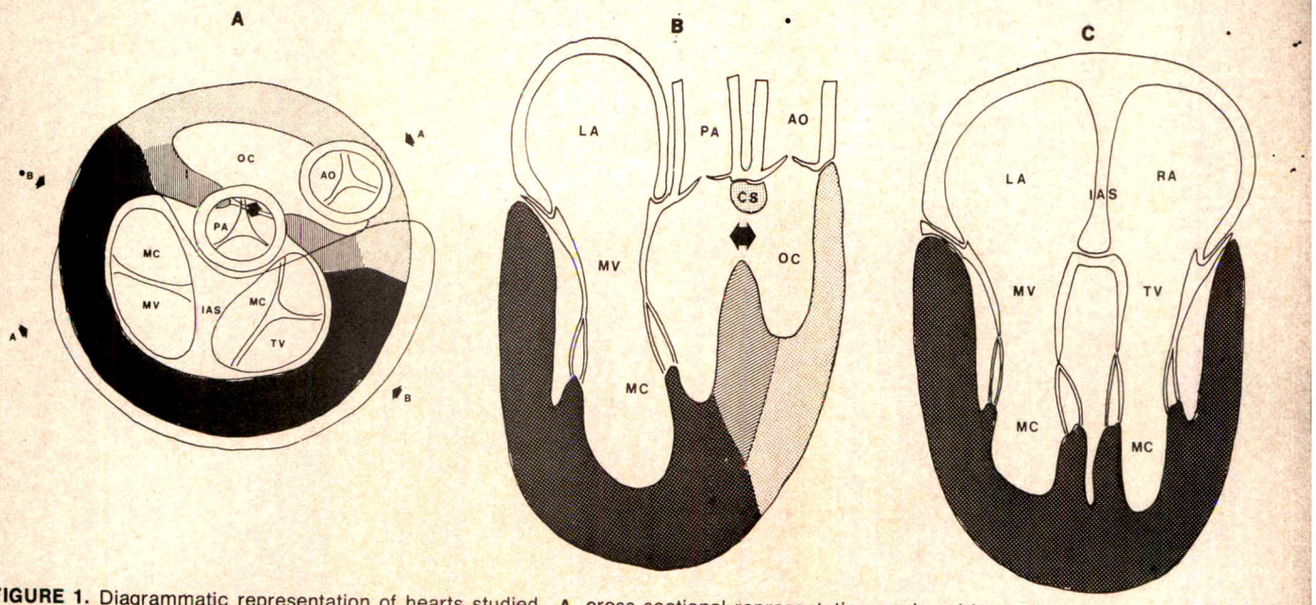

FIGURE 1. Diagrammatic representation of hearts studied. **A**, cross-sectional representation produced by superimposing the outlines of the great vessels, ventricular walls and atrial chambers. **B** and **C**, longitudinal sections taken in the planes A–A and B–B, respectively **(outer arrows** in **A). Inner arrows** indicate bulboventricular foramen. **Dark cross-hatched areas** indicate main chamber myocardium; **light cross-hatched areas** indicate outlet chamber myocardium; **striped areas** indicate septal myocardium. AO = aorta; CS = conal septum; IAS = interatrial septum; LA = left atrium; MC = main chamber; MV = mitral valve; OC = outlet chamber; PA = pulmonary artery; RA = right atrium; TV = tricuspid valve.

These points may seem to be of mainly academic interest, but recent experience in our center shows that they have far-reaching clinical significance. One of us (D.I.H.) recently attempted surgical correction of two univentricular hearts. The first heart was of the "common" ventricular type, in which the conducting tissue is reputed to lie on a posterior muscular ridge.[4] The anomaly was successfully corrected by avoiding this structure. The second heart was of the "single" ventricular type, in which specialized tissue is reported to be similarly situated. However, in this case a similar operative procedure produced traumatic heart block after inevitable suturing in the region of the foramen between the main and outlet chambers. This result indicated that further study of the specialized tissue is necessary in the "single" ventricular heart (type A of Van Praagh et al[1]). Such an investigation is further to be recommended since earlier workers had suggested that elucidation of the disposition of this tissue would clarify the nature of the chambers in such hearts. We have therefore taken appropriate hearts from the pathologic collection of the Royal Liverpool Children's Hospital and studied them histologically to define the course of the cardiac specialized tissue.

Materials and Methods

In view of the controversy concerning the nomenclature of univentricular hearts it is important to establish the morphologic features of the hearts studied in this investigation. We selected hearts corresponding to type A of Van Praagh et al.[1] or the "single ventricle with outlet chamber" of Lev et al.[2] Following the protocol of both these teams, we excluded hearts with atresia of an atrioventricular orifice but included hearts with an atrioventricular canal. Thus the specimens all had a main ventricular chamber that received both (or the common) atrioventricular orifices and gave origin to the posterior great artery (Fig. 1). We term this chamber the "main chamber." The anterior great vessel arose from a smaller chamber composed of ventricular myocardium, which we term the "outlet chamber." The tissue between the chambers is called the septum (Fig. 1).

Each heart was first studied to establish the morphologic characteristics of each chamber and the cardiac anatomy as a whole. To this end, each heart was photographed in anterior, posterior and internal views. All anomalies present were catalogued (Table I). Blocks of tissue were then removed for histologic investigation. When the size of the specimen permitted, the atrioventricular rings were removed in a single block of tissue, along with the septum between the chambers. In larger hearts two blocks were removed, comprising, first, the interatrial septum and adjacent ventricular myocardium and, second, the septum and bulboventricular foramen region. In some of the hearts incisions made at the original necropsies passed through these blocks; in others, all the structures were not present.

After removal, the blocks were prepared for sectioning by embedment in either paraffin wax or low viscosity nitrocellulose. Sectioning of the blocks was performed mostly in the frontal plane relative to the interatrial septum, but some specimens were cut in the transverse plane. Paraffin sections were cut in thicknesses of 10 μ, and low viscosity nitrocellulose sections in thicknesses of 20 μ. Originally 1 section in each 50 cut was mounted and stained by Masson's trichrome technique (1 in 5 for specimens embedded in nitrocellulose). After examination of these sections, additional sections were mounted and stained as required.

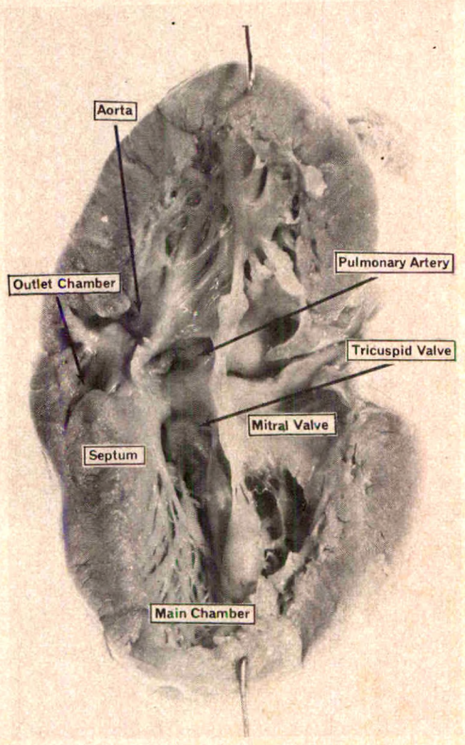

FIGURE 2. Morphologic features of typical hearts. Case 3 (D-loop, D-transposition). The heart has been opened by a cut through its sagittal plane, and is viewed from the left side. The small outlet chamber is anterior to the main chamber, and gives rise to the transposed aorta. Both atrioventricular valves and the pulmonary artery drain to or from the main chamber.

Results

Morphologic Findings

All the hearts studied manifested situs solitus and, as expected, the atrial chambers were in the solitus position. In every heart transposition of the great vessels was present, and the aorta lay to the front of the pulmonary artery. It was not always easy to decide if the aorta lay to the left or right, but we concluded in conjunction with study of the ventricular chambers that seven hearts were dextro-(D-) transposed and seven were levo-(L-) transposed. The main ventricular chamber formed the greater part of the ventricular mass (Fig. 2). The trabecular pattern was rather coarse, and typical fine trabeculae of the normal left ventricular sinus were rarely present. Two masses of papillary muscles were usually attached to each atrioventricular valve, and in several hearts the posterior muscles were fused together to form a prominent ridge of myocardium. It was often difficult to distinguish with certainty a tricuspid or bicuspid valve pattern in any given valve. In three hearts with D-transposition, chordae tendineae arose from the apex of the outlet chamber. These structures were usually paired and were muscular within the outlet chamber. Having traversed the foramen between the chambers, they inserted into the nearest cusp of the right atrioventricular orifice (Fig. 3). In one heart with L-transposition a small papillary muscle was present on the crest of the septum between the chambers, and chordae tendineae similarly arose from this structure to insert into the right atrioventricular valve; in another heart with L-transposition the papillary muscle arose within the outlet chamber. In a third heart with L-transposition one entire cusp of the left-sided valve arose from the outlet chamber and straddled the septum to reach the atrioventricular ring (Fig. 3D).

In all the hearts the foramen between the chambers was situated on the anterior wall of the main chamber, and the septal aspect of the main chamber was always nontrabeculated (Fig. 2). The foramen varied considerably in size but generally was larger in the hearts with L-transposition. One heart with D-transposition had no foramen, and left atrium and aorta were connected only by way of the pulmonary artery and a patent ductus arteriosus.

The outlet chamber was situated on the anterior aspect of the main chamber and in cases of D-transposition was located on the right shoulder of the heart; in cases of L-transposition it was situated on the left shoulder (Fig. 1). In all the hearts studied trabeculations were present in the outlet chamber, and in most hearts these extended for some distance below the level of the septum. Indeed, by using blunt dissection it was possible to define a potential chamber considerably below this level. The upper margin of the foramen between the chambers was composed of the conal septum, and the two limbs of this structure formed the lateral margins of the foramen. They merged with the septum between the chambers at their proximal ends. These muscular ridges were present in the outlet chamber of most of the hearts studied, but in some instances one of the ridges passed into the parietal wall of the main chamber.

Histologic Findings

The general disposition of the cardiac specialized tissue was identical in all the hearts studied (Fig. 4). The tissue was well differentiated in some hearts, less well differentiated in others, and in some hearts it was not possible to define all the structures to be described. We therefore discuss the general plan of the tissue, then its situation in several atypical hearts that warrant separate description. Other departures from the general plan in individual hearts are indicated in Table I.

Position of specialized tissue: *1. In the posterior interatrial septum (Fig. 5b, 6b).* This is the position in which one would expect to find the atrioventricular node. Examination of the region anterior to the coronary sinus revealed some specialized elements. These took the form of attenuated atrial cells that descended toward the fibrous ring. In this position they coalesced to form a small mass of bundles of cells compressed in a half oval against the fibrous ring by the attenuated atrial cells. This is the typical

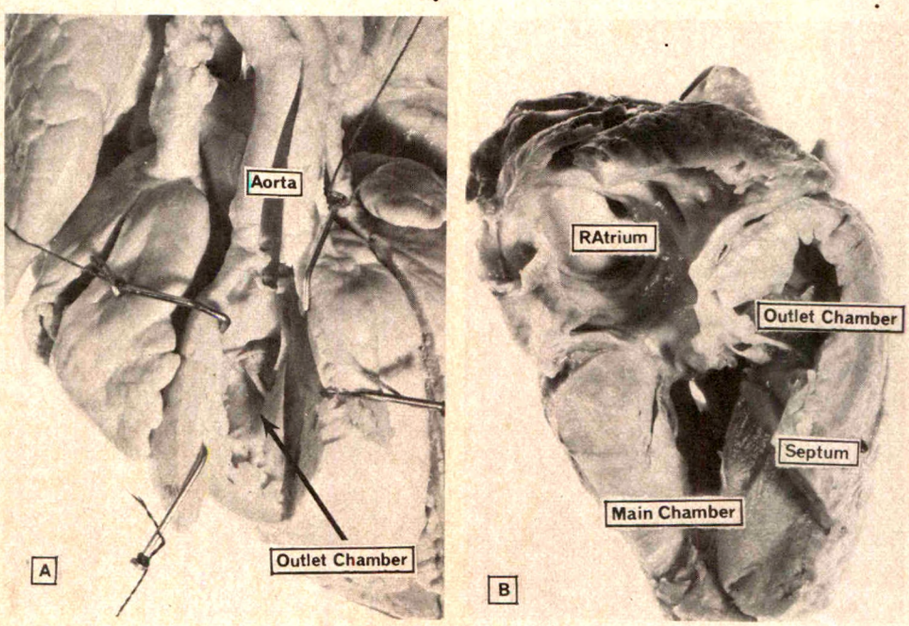

FIGURE 3. Two hearts exhibiting valvular tissue arising from the outlet chamber. **A,** Case 5. The small outlet chamber is opened from the front, and the chordae tendineae are seen passing through the foramen to the tricuspid valve in the main chamber. **B,** Case 7. The parietal wall of the right side of the heart has been removed. The outlet chamber is seen to be anterior to the main chamber, and chordae tendineae are clearly visible arising within the outlet chamber.

arrangement of the node, but in these hearts the mass of cells was much smaller than would normally be expected. When the cells were traced through serial sections, the specialized tissue gradually faded out, and the node made no contact with ventricular myocardium. Similarly, examination of the ventricular myocardium and subendocardium in this posterior region revealed no evidence of conducting tissues.

2. In the anterior interatrial septum (Fig. 5c, 6c, 7). Examination of this area revealed a second collection of atrial specialized cells. This area was situated at the anterior junction of the septum with the right atrial appendage, and medially it was related to the pulmonary arterial wall (in transposed position). As with the posterior node, the atrial cells became attenuated in this region both in the atrial septum and the wall of the appendage. These cells again joined together to form thick interwoven bundles of specialized tissue, again adjacent to the fibrous ring. In contrast to findings in the posterior node, when traced in serial sections this structure became continuous with the atrioventricular bundle, and this

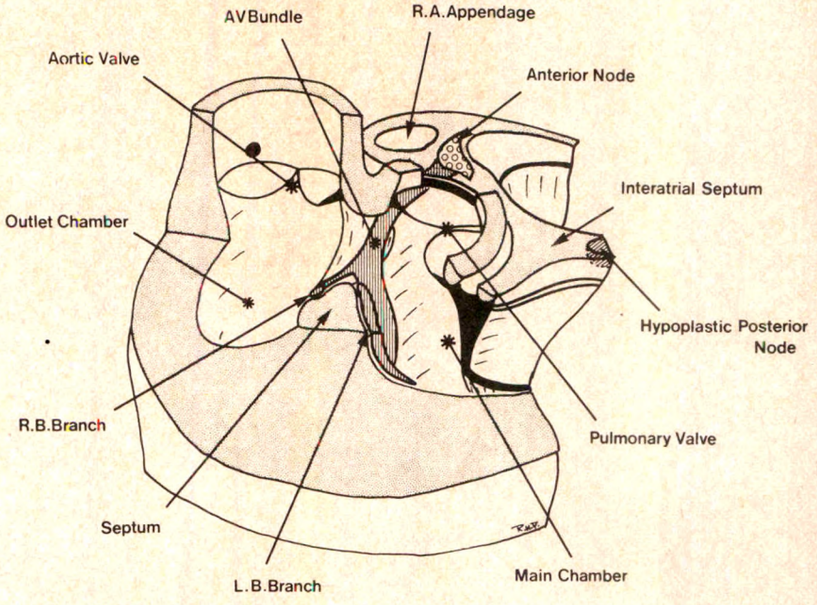

FIGURE 4. Diagrammatic representation of the position of the atrioventricular specialized tissue in the hearts studied. AV = atrioventricular; L.B. = left bundle; R.A. = right atrial; R.B. = right bundle.

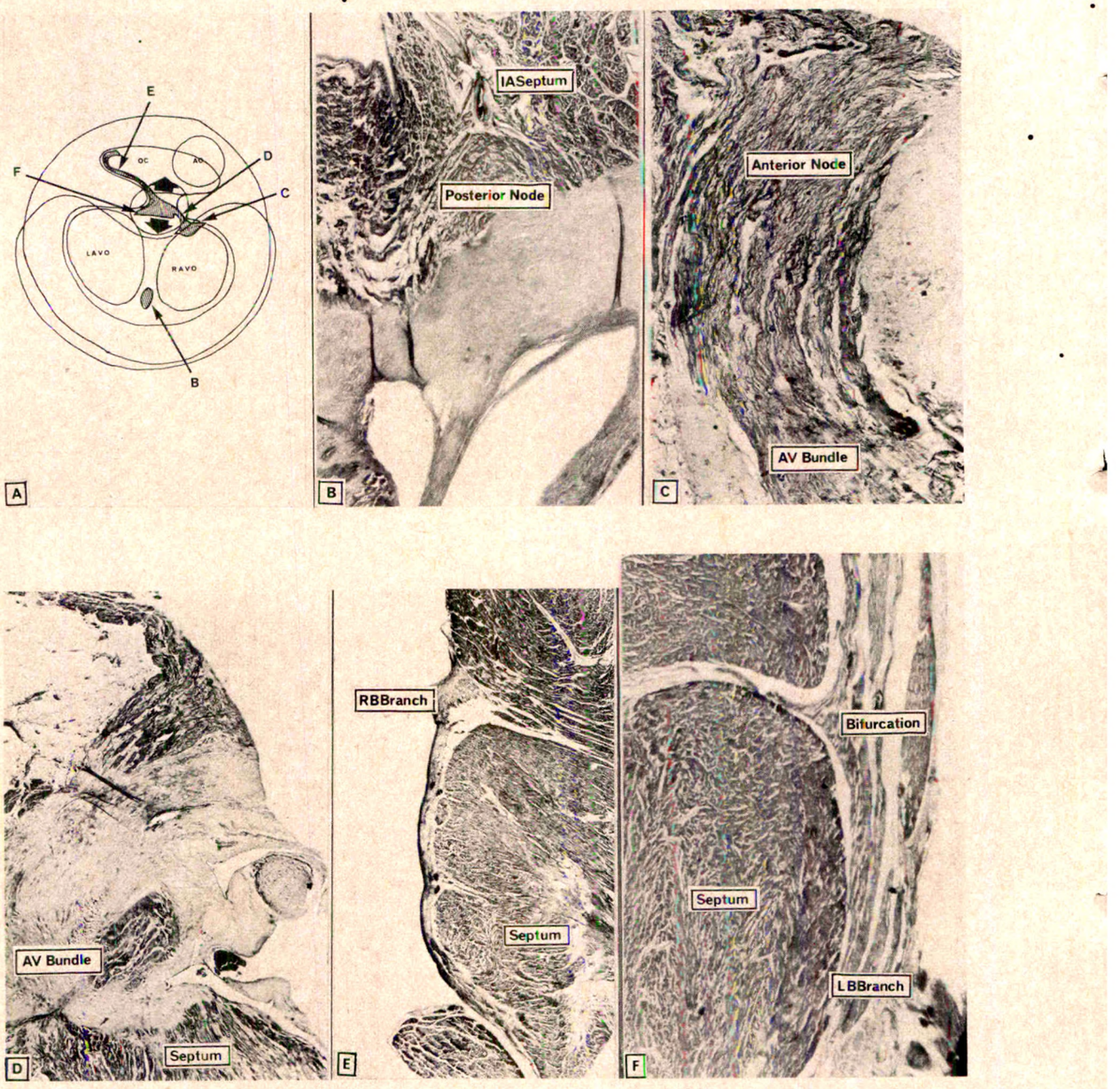

FIGURE 5. Case 2 (D-loop and D-transposition). Disposition of specialized tissue. **A,** diagrammatic cross section. **B** to **F,** photomicrographs taken from the appropriate points indicated in **A.** AO = aorta; AV = atrioventricular; IA = interatrial; LAVO = left atrioventricular orifice; LB = left bundle; OC = outlet chamber; RAVO = right atrioventricular orifice; RB = right bundle. **Arrows** indicate the foramen beneath the pulmonary artery; conducting elements are indicated by **cross hatching.**

was the only atrioventricular connection identified. We refer to this anterior collection of specialized tissue as the anterior node.

3. Atrioventricular bundle (Fig. 5d, 6d). This structure was directly continuous with the basal layer of cells in the anterior node. Having pierced the fibrous ring alongside the pulmonary valve ring, it came into contact with the right border of the foramen between the chambers. The bundle ran an extensive course down this right rim of the foramen, being situated on an aspect facing the main chamber.

4. Bifurcation and subendocardial specialized tissue (Fig. 5e, 6e). Having reached the level of the septum, the main portion of the bundle continued into the main chamber, expanding on the smooth-walled posterior aspect of the septum into a broad sheet of cells typical of the normal left bundle branch. At the level of the septum a smaller cord-like structure could be identified arising from the main bundle. In several hearts this structure arose at a higher level and descended through the myocardium to reach the outlet chamber. In all cases, having reached the outlet chamber, the cord-like structure rapidly expand-

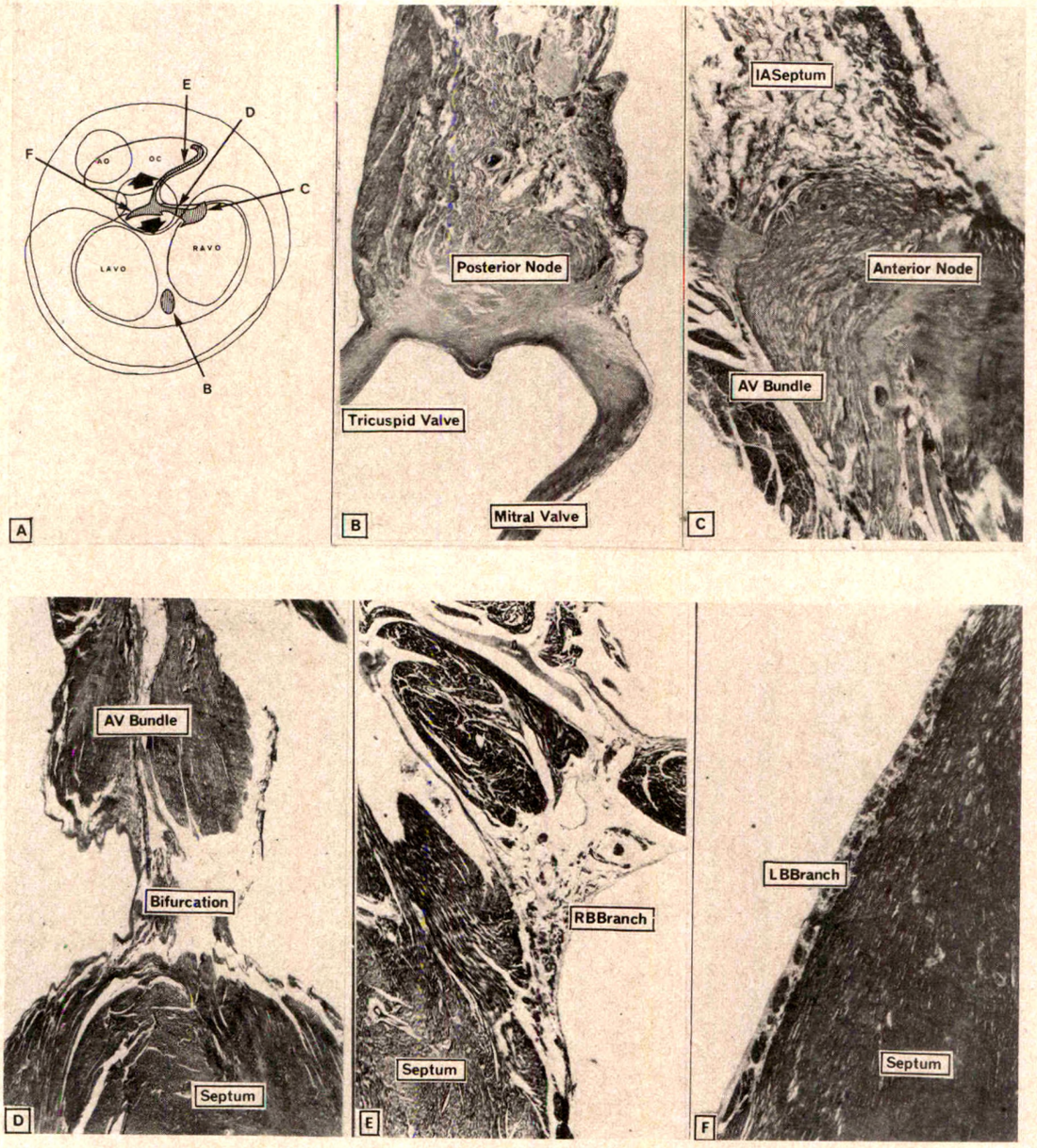

FIGURE 6. Case 10 (L-loop and L-transposition). Disposition of the specialized tissue. **A,** diagrammatic cross section; **B** to **F** photomicrographs from the appropriate points indicated in **A.** Abbreviations as in Figure 5. **Arrows** indicate the foramen beneath the pulmonary artery; conducting elements are indicated by **cross hatching.**

ed to form subendocardial ramifications. These conducting elements, typical of the right bundle branch, were identified within the outlet chambers of all the hearts studied.

Disposition in hearts with L-transposition (Fig. 4b, 6): The conducting tissue in these hearts was identical to that just described. Both posterior and anterior nodes were present, but only the anterior node made contact with the bundle. This bundle was again on the right border of the foramen, and descended in similar fashion. The left bundle-like structure passed into the main chamber, whereas the right bundle branch ran into the outlet chamber.

Hearts presenting with complete heart block: *1. Congenital.* Two hearts were in this category. In both, the general arrangement was similar to that described, but the various segments of specialized tissue were unconnected (Fig. 8). Thus, in one specimen, both atrial nodes were present, but neither made contact with ventricular myocardium. In the other specimen, which had an atrioventricular canal, a large segment of specialized tissue was confined to the atrial margin of the atrioventricular ring on its right side. In both hearts specialized tissue was identified astride the septum and in the subendocardium of both chambers. In the heart with two atrioventric-

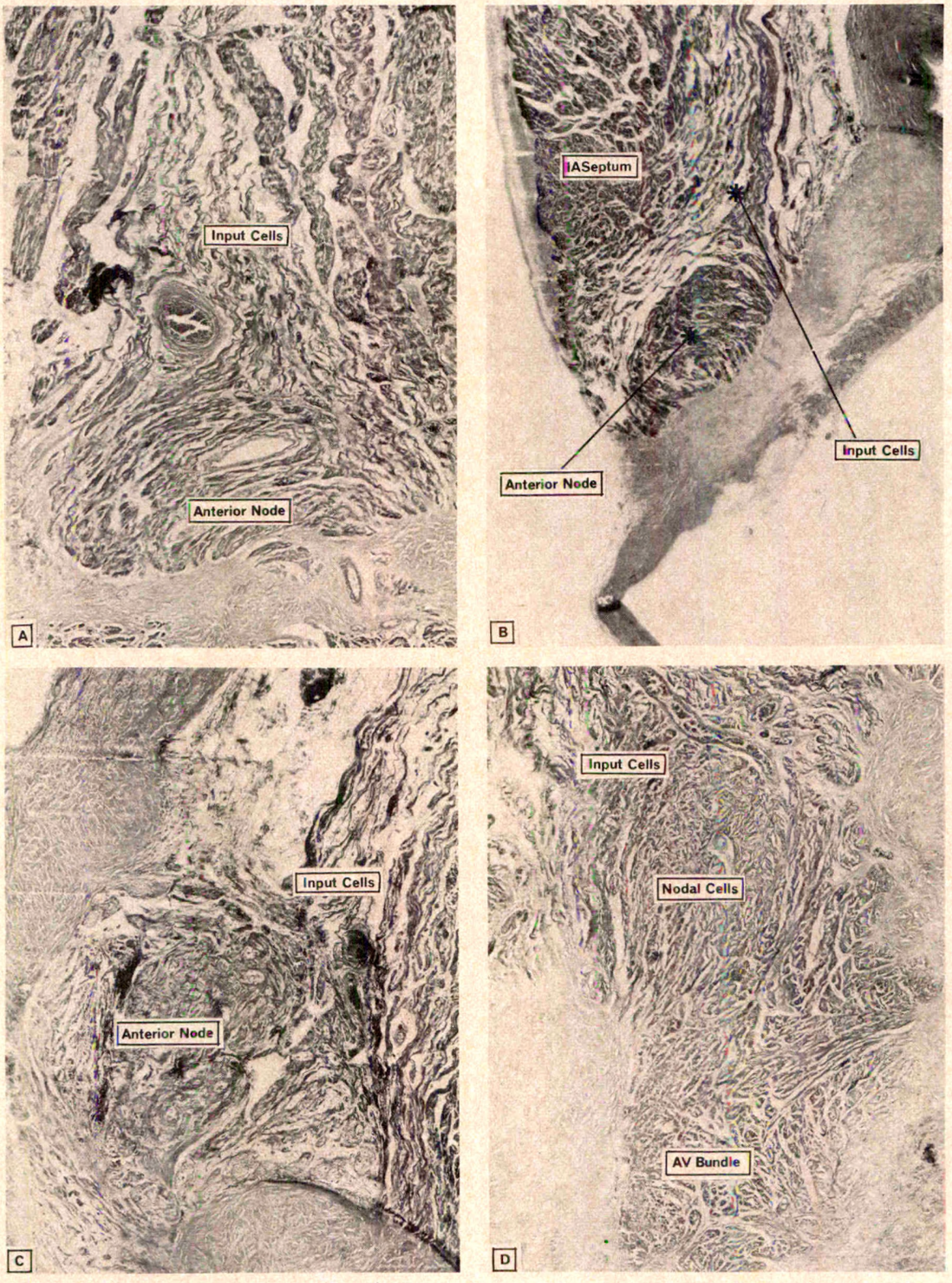

FIGURE 7: Higher power photomicrographs showing the structure of the anterior node. **A**, Case 4. **B**, Case 3. **C** and **D**, Case 14. Serial sections some distance apart. Abbreviations as in Figure 5.

ular valves it was also possible to identify atrioventricular bundles on each rim of the foramen between the chambers. However, each of these structures ended blindly, and made no contact with the atrial nodes.

2. Traumatic. The heart in which operative correction had been attempted comprised this category. L-transposition was present. As in the other hearts studied, the posterior node was identified in the interatrial septum and made no contact with the ven-

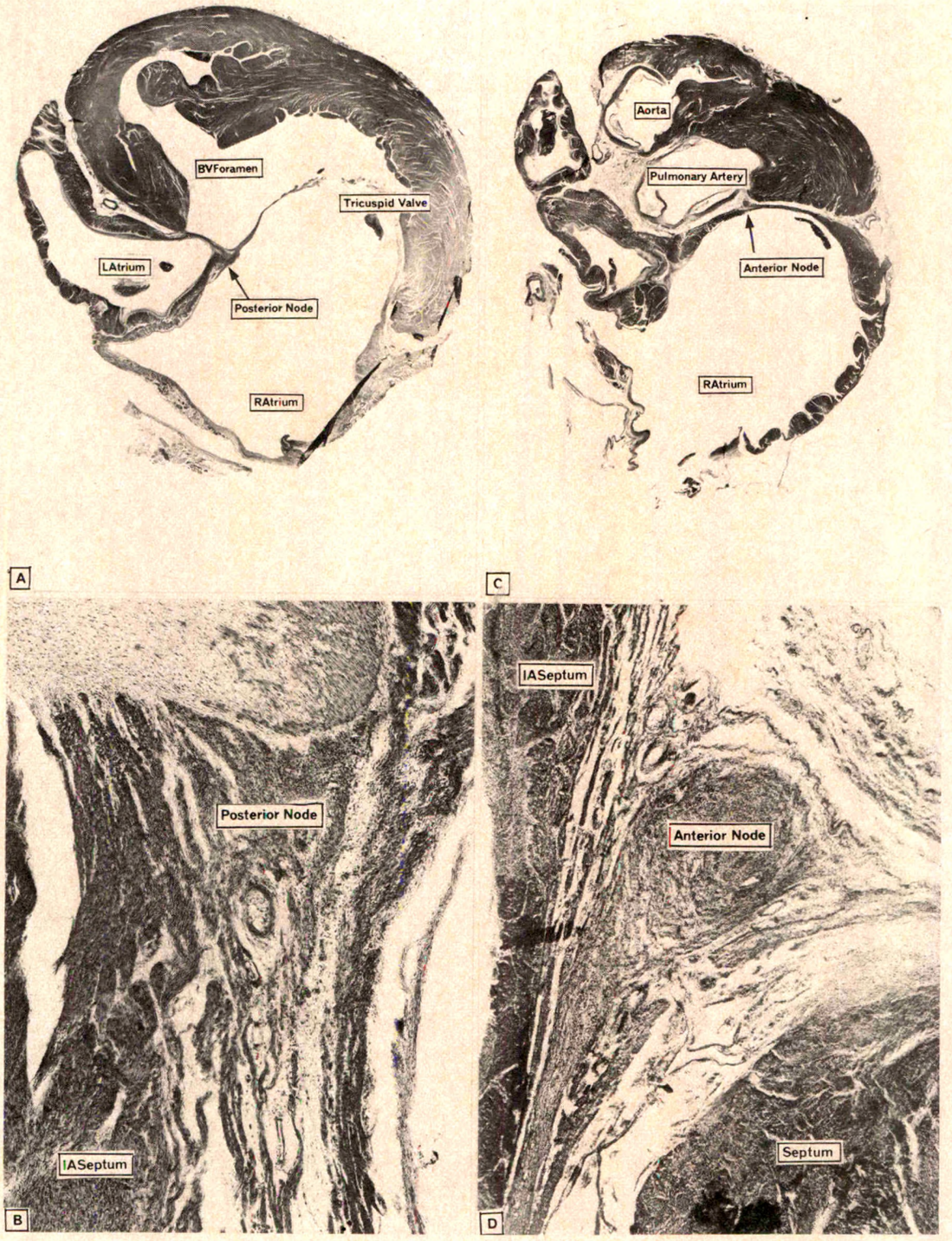

FIGURE 8. Case 12 (complete heart block). Disposition of specialized tissue. **A,** position of the posterior node (magnified in **B**). **C,** position of the anterior node (magnified in **D**). Neither node made contact with ventricular myocardium, which contained well formed specialized elements. BV = bicuspid valve; IA = interatrial; L = left; R = right.

tricular myocardium. The anterior portion of the heart was extensively traumatized, and it was not possible to identify the anterior node. However, the bundle was present, descending down the right rim of the bulboventricular foramen, and this structure bifurcated astride the septum. The conducting tissue in both chambers was extensively infiltrated with hemorrhagic exudate.

Hearts presenting with a short P–R interval and normal QRS complex: Four hearts in this cate-

gory were studied, and two had D-transposition. In each case, the specialized tissue was very well differentiated and was easy to follow. The anterior node was better developed than in most of the other specimens. Figures 5 and 6 are both taken from hearts in this group.

Heart with straddling atrioventricular orifice: One heart with this abnormality was studied. L-transposition was present. The posterior node was very poorly formed and made contact with ventricular myocardium. The anterior tissue was not identified in this specimen, but well formed bundle branches and their ramifications were present in both the main and the outlet chambers.

Discussion

Surgical implications of differentiating "single" and "common" ventricle: Our investigation has established that the specialized tissue is unexpectedly situated in hearts of the "single" ventricular type (type A of Van Praagh et al.[1]). This finding has implications for both clinical practice and the morphology of the anomaly. First, review of the literature indicates that the situation we describe differs from that previously reported by Lev[4] in single ventricular hearts. This brief report suggested that the tissue was located on a posterior muscular ridge in both "single" and "common" ventricles. Such a situation is to be expected in the "common" ventricular heart, since this malformation represents a huge ventricular septal defect, and the posterior position of conducting tissue in the bulk of such anomalies is well documented.[5-7] Our operative experience also confirms such a position in "common" ventricle. In "single" ventricle our findings show that the tissue is not situated astride a posterior ridge. Indeed, in the hearts we studied, the fused posterior papillary muscles were the only structures we could identify as approximating such a ridge. In fact, the tissue lies astride the septum, and the connecting atrioventricular bundle descends down the right rim of the bulboventricular foramen, having perforated the fibrous ring to the right of the posterior great vessel. It is therefore vital to distinguish between "single" and "common" ventricle before embarking upon corrective surgery in univentricular hearts since the area "at risk" differs in the two subgroups.

Our experience suggests that repair of the defect in "single" ventricle without suturing on the right side of the foramen is likely to prove extremely difficult when the anomaly is associated with transposed great vessels. Although we are still studying this aspect of the problem, we recommend caution in subjecting such hearts to operation, since there is every likelihood of producing complete block during the corrective procedure. However, if "single" ventricle is associated with nontransposed great vessels, as in the so-called "Holmes" hearts,[8] then it may well be possible to produce correction without impinging upon the right rim of the bulboventricular foramen. This, of course, presupposes that the specialized tissue is similarly arranged in such hearts. Clearly, the surgeon would be helped if he knew the precise type of univentricular heart he was to repair before he entered the chest. Our clinical records show that the diagnosis of univentricular heart with outlet chamber was initially difficult to make, but most of the cases were investigated several years ago, and retrospective study of the angiograms showed that the outlet chamber was visible in most hearts. With modern radiologic techniques in specialized centers, exact diagnosis should be feasible.

Mode of development of specialized tissues: We consider that from a developmental viewpoint the relevant findings of our investigation are the presence of: (1) a hypoplastic posterior node making no ventricular connection, (2) a well formed anterior node establishing atrioventricular communication, and (3) an anterior bifurcation, with the right bundle branch always present in the outlet chamber.

The posterior node is present in the interatrial septum and is related to the coronary sinus. It therefore seems reasonable to propose that this structure represents the atrophic atrioventricular node of the normal heart, which is considered to be derived from either left sinus horn tissue[9] or atrioventricular canal musculature.[10] Documentation of anterior nodes in the human heart is very rare; to the best of our knowledge the only examples are those in the case described here and in the cases cited by Lev et al.[11] No cases have been described with sole atrioventricular communication through an anterior node. However, a recent study[12] of development of human specialized tissue showed that the atrioventricular node develops in strata, and that the lowest stratum and the atrioventricular bundle are developed as one single unit. Furthermore, the development of this unit is intimately related to the development of the posterior portion of the interventricular septum, whereas the bifurcation and bundle branches are developed in relation to the anterior, bulboventricular, part of the septum.

Most important, however, was the finding that an annulus of specialized tissue was present in the distal margin of atrial musculature at its insertion into the tricuspid valve base, and that this annulus was expanded into a second node-like structure anteriorly. Although this was originally described as a lateral structure,[12] reexamination of the fetal specimens together with examination of normal human neonatal hearts (unpublished observations) shows that the anterior node is present at the junction of the anterior interatrial septum with the atriobulboventricular ledge tissue, and that it is separated from the normal bifurcation only by the fibrous annulus and some conal septal musculature (Fig. 9A). Furthermore, identical specialized tissue is present in adult rats, rabbits and guinea pigs,[13,14] and similar tissue has been previously reported in the embryonic calf.[15] Although in the normal heart this tissue does not form an atrioventricular connection, we believe that in the hearts described here it forms the abnormally situated anterior atrioventricular connection. This is because in "single" ventricle with outlet chamber

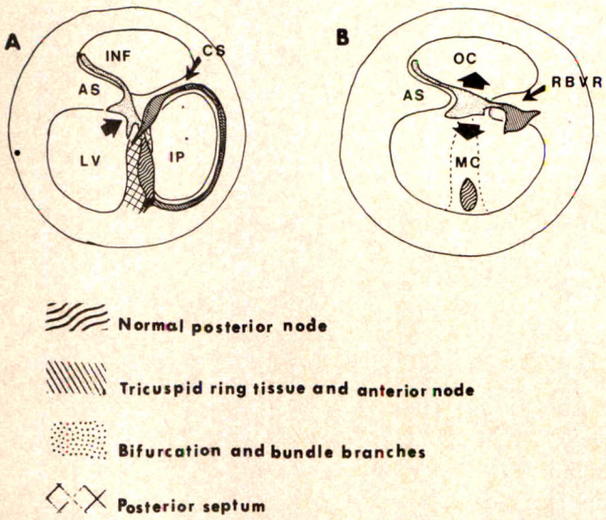

FIGURE 9. Diagrams to show postulated mechanism of production of anterior atrioventricular connection. **A,** the normal situation with the atrioventricular node astride the posterior septum, which brings it into contact with the bifurcation and bundle branches. However, the tricuspid ring tissue and anterior expansion are always present in the fetal heart. **B,** in "single" ventricle with outlet chamber, the posterior septum is either absent or malpositioned. Therefore the posterior node is unable to contact the bifurcation. The connection is effected through the anterior expansion of ring tissue which becomes the anterior node. AS = anterior septum; CS = crista supraventricularis; INF = infundibulum; IP = inlet portion right ventriculer; LV = left ventricle; MC = main chamber; OC = outlet chamber; RBVR = right bulboventricular ridge. **Thick arrow** in **A** = position of bulboventricular foramen.

the posterior interventricular septum is either absent or misplaced. The lower nodal-atrioventricular bundle unit is therefore unable to connect the posterior node with the ventricles. In contrast, the interatrial septum, atriobulboventricular ledge and anterior interventricular septum are in relatively normal positions. It is therefore easy for the embryonic anterior node to effect connection with the normally situated bifurcation and branches and produce the situation described here (Fig. 9B).

If this concept is correct, then a heart with both nodes present would be a developmental possibility, with both nodes making atrioventricular connections. We have described such an arrangement of conducting tissue in an unusual form of double outlet right ventricle, in which the two nodes formed two bundles that merged into a common bundle before bifurcating to supply the ventricles.[16] Confirmatory evidence of the validity of our concept is provided by study of hearts with classically corrected transposition. Walmsley[17] suggested that the sinistral loop of such hearts carried the ventricular specialized tissue an excessive distance away from the node, and he explained the high incidence of heart block in these cases on such grounds. The case of Lev et al.[11] and our two cases with complete block demonstrate that the anterior node, although well developed, is also unable to establish contact. However, we have also examined a case of classic corrected transposition with normal conduction tissues in which the situation of the specialized tissue was identical to that described here, with contact occurring by way of the anterior node (unpublished observations). Thus we consider that the abnormally situated tissue in "single" ventricle is an overgrowth of the specialized tissue always present in the normal heart and that this overgrowth is caused by failure of development of the posterior portion of the interventricular septum.

Morphogenesis of univentricular heart: Our morphologic and histologic findings are relevant to the morphogenesis of the anomaly, which is highly controversial and inextricably linked with the controversy surrounding the origin of the right ventricle of the normal heart. Pernkopf and Wirtinger, and Goertler (quoted by Lev et al.[2]) believed that the primitive ventricle was septated to produce the inflow portions of both ventricles, whereas the outflow tracts were formed from the conotruncus. Application of this theory to "single" ventricle suggests that the posterior interventricular septum is absent, and that the septum is either a pseudo-septum of conal ridges[18] or a persistence of the bulboventricular ridges (the latter interpretation was made by Harley[19] after an extensive review of the literature). In contrast, studies performed at the Carnegie Institute[20,21] showed that the trabeculated pouch of the right ventricle was a bulbar structure and that the entire bulboventricular septum became the interventricular septum after rightward migration of the atrioventricular canal. Thus, de la Cruz and Miller[3] consider that "single" ventricular hearts represent lack of atrioventricular canal migration—hence their term "double inlet left ventricle." Van Praagh and associates also adopt this concept, but they consider that the right ventricular sinus is absent and that the outlet chamber is infundibulum. They do believe that the septum is true interventricular septum.

Both Lev et al.[2] and Van Praagh et al.[1] suggest that study of conducting tissue can elucidate this problem. However, either concept can explain the disposition described because the conducting elements are normally formed astride the anterior septum, and this is a bulboventricular structure in either concept of development. Similarly, the continuity between posterior node and bifurcation may be lacking either because the posterior septum is not formed or because it is misplaced. The presence of the atrioventricular bundle on the right edge of the bulboventricular foramen tends to favor the concept of lack of migration.

Review of our morphologic findings is also inconclusive. The presence of different trabeculated patterns on either side of the main chamber and normal attenuation of the atriobulboventricular ledge with centralization of the posterior great vessel favor the hypothesis of Lev[2] and Harley.[19] However, the presence of valvular elements in the outflow chambers of some hearts, together with trabeculation of these chambers, supports the concept of de la Cruz and Miller.[3] On examination of embryos and other malformed hearts we find no evidence of separate growth

of anterior and posterior portions of the ventricular septum; absence of such evidence contends against the ventricular septation hypothesis. On theoretical grounds we are also unable to understand how the right atrioventricular canal migrates to contact the bulbus without a sleeve of ventricular myocardium being incorporated into the right ventricle. Thus, on the evidence available, we are unable to decide which hypothesis is correct. We are now investigating a series of hearts with juxtaposition of the atrial appendages, generally agreed to indicate a primitive state of the bulboventricular loop. These hearts may provide vital evidence. In addition, we believe that accurate study of embryos in horizons XIII to XVI would elucidate the mode of migration of the atrioventricular canal. Accurate illustration and description of this event is singularly lacking in the account of de Vries and Saunders.[21]

In conclusion, we endorse the opinion of Lev et al.[2] that in our present state of knowledge it is preferable to refer to these hearts simply as "primitive" ventricles. We also believe that it is necessary to indicate whether there is an outlet chamber since presence of this feature indicates that the specialized tissue will occur in the abnormal situation described.

Acknowledgment

We acknowledge with gratitude the help received from Professor J. D. Hay and Dr. J. Shackleton, and their kind permission to study cases previously in their care. We are also indebted to Dr. A. E. Becker of Wilhelmina Gasthuis, Amsterdam, who kindly read and criticized an earlier manuscript. The technical procedures were excellently and carefully performed by Mrs. A. Smith, and photographic material is the work of Messrs. K. Walters and R. Wylie.

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Updating Sphygmomanometry

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The measurement of systemic blood pressure using a sphygmomanometer and stethoscope is well entrenched in medical practice. As a noninvasive tool for the rapid determination of intraarterial pressure, the technique has proved accurate and reliable most of the time—that is, if one has no interest in the obese, the very young, those with shock or those whose upper limbs are unusually conically shaped and thus adapt poorly to standard cuffs. With the exploding technology of the past two decades one would have expected a more precise technique to have evolved for the noninvasive assessment of systemic blood pressure. But except for a few abortive flourishes in automation, blood pressure measurements are obtained in much the same manner as in grandfather's day. Today, needless to say, the errors inherent in the technique are no less nettlesome.

In the generally accepted procedure of sphygmomanometry, after inflation of the pneumatic bladder, the intrabladder pressure, as measured by either an aneroid or mercury manometer, is assumed to be identical to pressure applied to the artery wall by the compressed tissues. After deflation of the bladder, the onset of tapping sounds (Korotkoff sounds[1]) heard through the stethoscope is taken as a sign of peak systolic brachial pressure and the cessation or muffling of the sounds is the sign of end-diastole. Too often, unfortunately, these signs fail to signal true systole and diastole. On closer examination of the procedure, we find that this error stems from two principal sources: (1) inaccurate transmission of bladder pressure to the artery wall due to the design of the cuff-bladder assembly and, (2) lack of understanding of the relation of Korotkoff sounds to the systolic and diastolic end-points, resulting in their improper detection. Although faulty instrumentation and clumsy technique cannot be ignored as frequent causes of error, their elimination is simpler than elimination of the problems of cuff and sound, which requires a better understanding as a prerequisite.

Von Recklinghausen[2] in 1901 is reputed to have been the first to propose changing the design of the sphygmomanometer cuff to improve accuracy in blood pressure measurement. However, after 70 years of attention focused on the problems surrounding the choice of the ideal sphygmomanometer cuff, a satisfactory and universally acceptable product has not been developed. The principal reason for this failure is the lack of information on the conditions necessary for the accurate transmission of bladder pressure to the artery wall; consequently, a blood pressure cuff that can reliably satisfy these conditions has not been designed. The 1967 American Heart Association recommendations for human blood pressure determination[3] proposed a pneumatic bag 20 percent wider than the diameter of the limb on which it is to be used. With respect to length, it was suggested that the bag should go halfway around the limb, but be placed directly over the compressible artery. These recommendations have not been updated although there is now convincing evidence that a revised set of standards for the pneumatic bag are in order.

Recommendations for occlusive cuff and pneumatic bag: From a series of experiments performed in our laboratory on an upper arm-brachial artery hydromechanical analog,[4] and from analytic studies,[5] we have concluded that intrabladder pressure is transmitted with least decay to the underlying compressible artery when the length of the pneumatic bag is such that it completely encircles the model arm. The conclusions drawn from these studies have substantial support in data derived from human studies in a number of laboratories, including our own. The results of studies carried out by King,[6] Karnovin[7] and others[8-10] support the view that a completely encircling pneumatic bladder is preferable to any abbreviated version. The compromise that we indulge in today of employing a short inner bladder and an outer sleeve of so-called stiff fabric seems to be less of a compromise than an open invitation to error.

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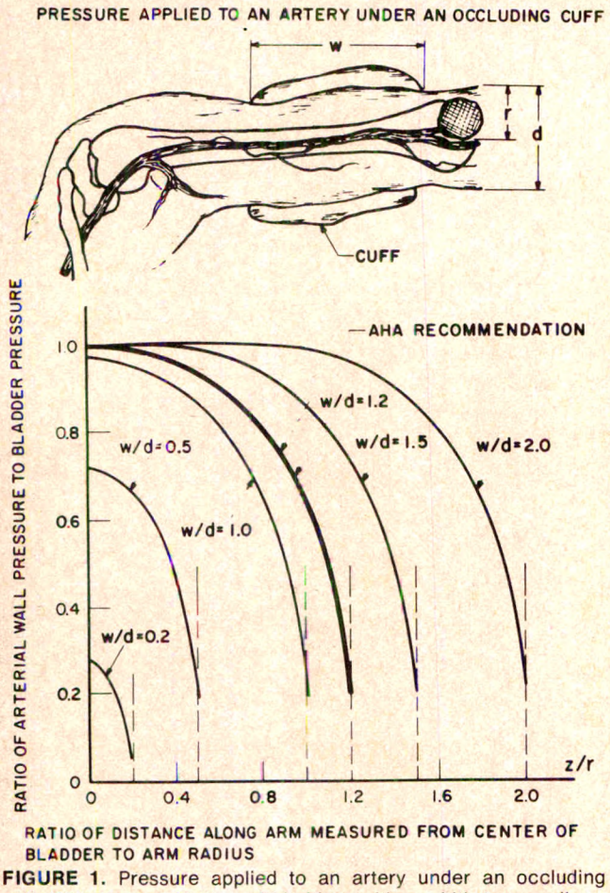

FIGURE 1. Pressure applied to an artery under an occluding cuff. With the application of bladders with a width to arm diameter ratio (w/d) ranging from 0.2 to 2.0, it is found that at w/d = 1.2 the arterial wall pressure reaches the bladder pressure value at one point on the artery under the center of the cuff (z = 0). As w/d is increased, a longer length of the artery is exposed to the full cuff pressure, but no segment of artery is ever subjected to a pressure greater than the bladder pressure. Analytic studies, therefore, negate the view that wide bladders cause underestimation of arterial pressure. d = diameter of arm; r = radius of arm; w = width of bladder; z = distance along arm measured from center of bladder.

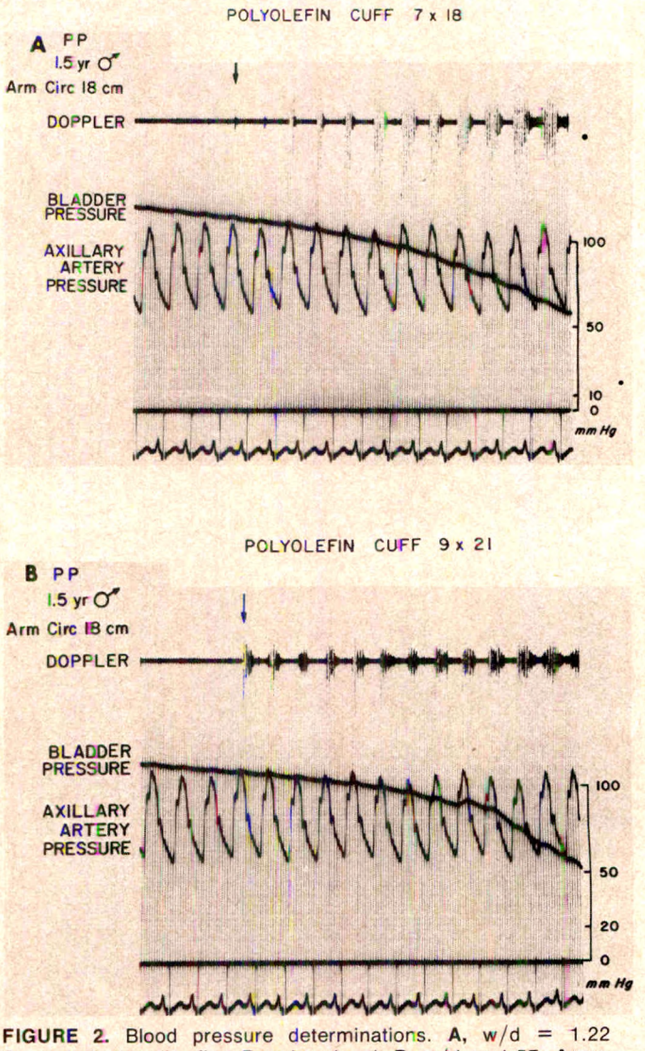

FIGURE 2. Blood pressure determinations. **A,** w/d = 1.22 **Arrow** indicates the first Doppler signal. **B,** w/d = 1.57. **Arrow** indicates the first Doppler signal. d = arm diameter; w = bladder width.

With respect to determining the optimal width of the pneumatic bag, it has been well documented in clinical studies that very narrow bladders yield inordinately high systolic and diastolic values at all age levels. However, no physically sound explanation has been previously presented for this phenomenon. Recently, analytic studies[5] have determined that constraint of longitudinal arm tissue motion is associated with accurate pressure transmission to the artery wall. These studies have also predicted the minimal ratio of bladder width to arm circumference for accurate pressure transmission to at least a point on the artery under the center of the cuff. The American Heart Association recommendation of a bladder width 20 percent greater than arm diameter ($1.2/\pi$ × arm circumference) accords very well with these analytic results as a minimal requirement (Fig. 1). However, in a number of clinical experiences, for example, with the upper arm of small infants, the long thin upper arm of the tall adolescent, and the broad tapered upper arm of the very obese, bladder widths 1.2 × arm diameter yield systolic and diastolic values considerably higher than those of simultaneously recorded intravascular pressures. In our patient sampling, a bladder width that complied with the Heart Association recommendation produced a narrow cuff effect, indicating that these minimal requirements should be exceeded to ensure accurate measurement (Fig. 2). In both human and analog experiments in which wider bladder widths were tested, peak systolic values failed to show the marked discrepancies noted with narrow bladders. In the majority of instances, the correspondence between direct and indirect peak systolic pressures was identical or nearly so. In human investigations, unusually wide bladders, extending from the axilla to a level 1 or 2 cm above the antecubital crease, failed to elicit previously reported low peak

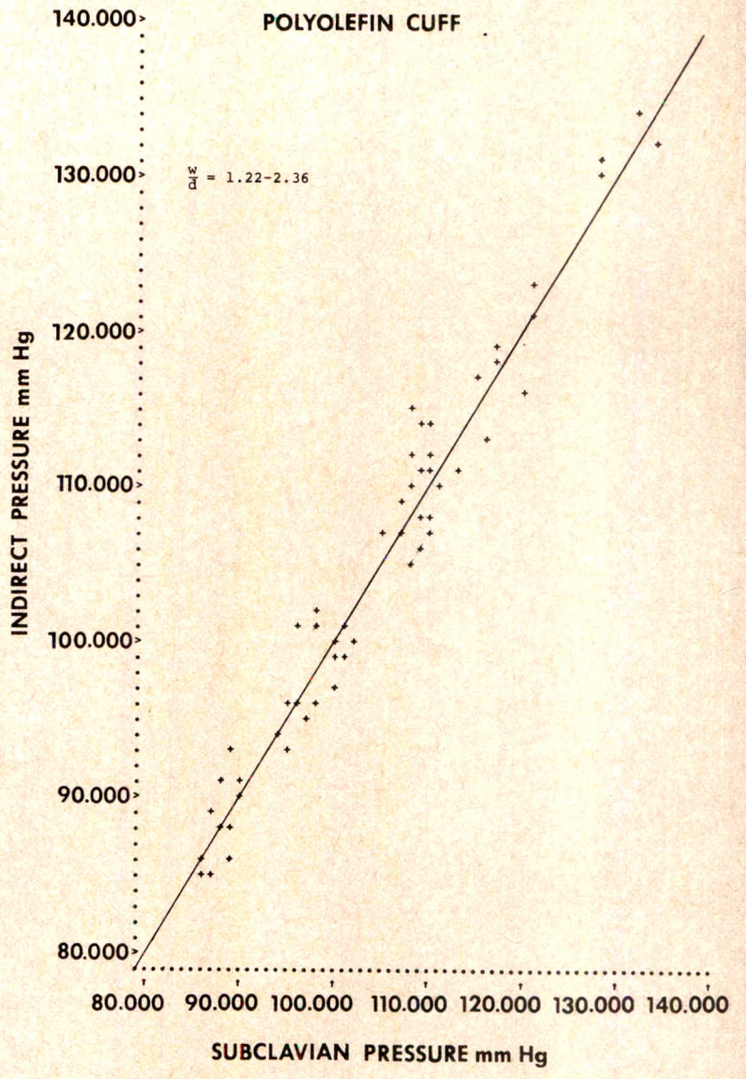

FIGURE 3. Comparison of direct and indirect use of peak systolic pressure measurements obtained with polyolefin cuffs. Indirect peak systolic pressure measurements were obtained using polyolefin cuffs with a width to arm diameter ratio ranging from 1.22 to 2.36. Arterial peak systolic pressures were measured with a catheter tip at the subclavian-axillary artery junction. The center diagonal is the line of identity, and the light parallel lines are +3 mm Hg. The seven instances in which indirect pressures were noted to exceed the 3 mm error were measurements obtained using polyolefin cuffs with a width to arm diameter ratio of approximately 1:2 (American Heart Association recommendation).

systolic values[3] when direct and indirect pressures were compared. These clinical results are in agreement with the analytic prediction of the nonexistence of the so-called "wide cuff effect."[5] Indications of the production of Korotkoff sounds in our studies, however, were sensed with a Doppler ultrasonic transducer rather than with a stethoscope. Poor signal pickup with a stethoscope may actually account for the low values previously reported with the application of wide cuffs to the upper arm.

We have come to realize that the one or two different bladder-cuff sizes used for blood pressure measurement in the adult and the few models available for infants and children are inadequate to achieve the levels of accuracy and reliability possible with this technique. The goal now would appear to be a pneumatic bladder that completely encircles the limb and that has a minimal width to length ratio of approximately 1:3, with an option for greater width to length ratios when circumstances demand. For the conically shaped obese arm or leg, the rectangular configuration should be replaced by a bladder of trapezoidal design so that, when applied to the limb, it would conform more closely to its natural contours. In effect, we are suggesting an individualized pneumatic bladder prescription which might be accomplished with the aid of a sphygmomanometer bladder kit containing a variety of bladder sizes and types. If this seems unnecessarily tedious, it is no more so than for the ophthalmologist, for example, who refracts eyes with a battery of lenses at his disposal rather than with a few choice pieces.

Relation of Korotkoff sounds to systolic and diastolic pressure levels: Unfortunately, the matter of the choice of a proper occlusive cuff is only a portion of the solution to the problem of improving the accuracy of sphygmomanometry. The relation of the Korotkoff sounds to the systolic and diastolic pressure levels must be appreciated. These sounds have at various times been attributed to a water hammer effect,[11] fluid shock wave propagation,[12] turbulent motion of the blood[13] and oscillations of the arterial wall.[14,15] It is obvious that the major component of the sounds cannot be associated with all of these

phenomena. It is necessary to determine which component of the Korotkoff sound production is of interest in blood pressure determination and how these sounds relate to the physiologic events occurring under the cuff.

Korotkoff sounds reproduced in an arm analog have been found to be virtually identical to their in vivo counterparts.[4,16] This analog has been used as a tool to investigate the probable origins of the Korotkoff sound production. Simultaneous recordings were made of the audible sounds, the oscillation of the arterial wall and the arterial blood flow velocity. This was accomplished by sensing with a crystal microphone and a Doppler ultrasound transducer in both analog and human studies. Frequency analyses of these signals have shown that the arterial wall oscillations cause the major component of the Korotkoff sounds. The first arterial wall oscillations begin at the moment intrabladder pressure drops below peak intravascular pressure and terminates when intrabladder pressure dips below end-diastolic pressure.

The vibrating arterial wall normally gives rise to sounds detectable with a stethoscope. Unfortunately, these sounds are often not discernible in human subjects because their frequency or amplitude, or both, lie below the range of human audibility. This becomes most apparent in attempts to determine blood pressure in small infants, in some obese adults and in subjects with shock. Consequently, one would prefer to sense the arterial oscillations at their source rather than listen to the sounds produced by those oscillations. A suitable filtered and properly positioned Doppler ultrasonic transducer is far more sensitive in directly detecting arterial wall oscillations than is a stethoscope in indirectly sensing these oscillations by picking up Korotkoff sounds. At present, in human studies employing the ultrasonic transducer in place of a stethoscope, extremely accurate measurements of peak systolic pressures are obtainable. The determination of end-diastolic pressure, however, is more difficult since appropriate conditioning of the ultrasonic signal is necessary to isolate the arterial wall oscillations at end-diastole from the blood flow signal which is also sensed by the Doppler system. Instrumentation now available is capable of this discrimination.

Recommended method for sphygmomanometry: In conclusion, we recommend that indirect blood pressure measurement by sphygmomanometry be performed with a properly designed and sized cuff-bladder assembly as described and an appropriate arterial oscillation sensor. A variety of such systems have been under investigation and evaluation over the past several years by many investigators. For the past 2 years, in our laboratory, we have been developing and clinically testing an integral pneumatic cuff-bladder assembly made of a heat-sealable polyolefin film. This assembly has been designed to satisfy the conditions necessary for accurate bladder pressure transmission to the artery wall. It has been made available by the manufacturer in all desired lengths, widths and configurations and can be produced sufficiently inexpensively to be disposable. A relatively inexpensive, commercially available Doppler ultrasound system has been used in our studies and has been found to be adequate to our needs. In the tests performed to date on a variety of hypotensive, normal and hypertensive patients, ranging in size from a 1,000 g premature infant to a 280 lb adult, it has been found possible to make indirect blood pressure determinations accurately and reliably in situations in which the stethoscope-commercially available cuff system is completely inadequate (Fig. 3). This method is valuable in situations in which it was previously impossible to determine blood pressure indirectly. However, it is most valuable in cases in which use of the traditional method yields inaccurate measurements.

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Circulatory reflexes from mechanoreceptors in the cardio-aortic area. Pelletier CL, et al.
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Preservation of the heart. Proctor E.
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HEART AUSCULTATION

Mitral valve prolapse--Click syndrome. Jeresaty RM.
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Nutr Rev 29:10-1, Jan 71 (5 ref.)

HEART ENLARGEMENT

Structural conditions in the hypertrophied and failing heart. Spotnitz HM, et al.
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HEART FAILURE, CONGESTIVE

Alterations of cardiac sympathetic neurotransmitter activity in congestive heart failure. Rutenberg HL, et al. **Am J Cardiol** 32:472-80, 20 Sep 73 (49 ref.)
Abnormal biochemistry in myocardial failure. Schwartz A, et al. **Am J Cardiol** 32:407-22, 20 Sep 73 (86 ref.)
Structural conditions in the hypertrophied and failing heart. Spotnitz HM, et al.
Am J Cardiol 32:398-406, 20 Sep 73 (41 ref.)
New developments and therapeutic applications of cardiac stimulating agents. Williams JF Jr.
Am J Cardiol 32:491-6, 20 Sep 73 (46 ref.)
Peripheral circulatory control mechanisms in congestive heart failure. Zelis R, et al.
Am J Cardiol 32:481-90, 20 Sep 73 (77 ref.)
Cardiovascular complications of chronic bronchitis and emphysema. Bishop JM.
Med Clin North Am 57:771-80, May 73 (37 ref.)

HEART, MECHANICAL

Blood oxygenation in extracorporeal devices: theoretical considerations. Spaeth EE.
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HYDRALAZINE

Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. Perry HM Jr.
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HYPERTENSION

Vascular reactivity in systemic arterial hypertension. Mendlowitz M. **Am Heart J** 85:252-9, Feb 73 (70 ref.)
Correlation of pathophysiology and pharmacotherapy in primary hypertension. Koch-Weser J.
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Hypertension and human renal prostaglandins. Vance VK, et al. **Med Ann DC** 42:419-22, Sep 73 (31 ref.)
Renomedullary interstitial cells (RIC), prostaglandins (PG) and the antihypertensive function of the kidney. Muirhead EE, et al.
Prostaglandins 3:581-94, May 73 (30 ref.)

HYPERTENSION, PULMONARY

Cardiovascular complications of chronic bronchitis and emphysema. Bishop JM.
Med Clin North Am 57:771-80, May 73 (37 ref.)

HYPERTENSION, RENAL

Hypertension, natriuresis and the renomedullary prostaglandins: an overview. Lee JB.
Prostaglandins 3:551-79, May 73 (46 ref.)

LUPUS ERYTHEMATOSUS, SYSTEMIC

Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. Perry HM Jr.
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MITRAL VALVE INSUFFICIENCY

Mitral valve prolapse--Click syndrome. Jeresaty RM.
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MYOCARDIAL DISEASES, PRIMARY

Hypertrophic diseases of the myocardium. Goodwin JF.
Prog Cardiovasc Dis 16:199-238, Sep-Oct 73 (83 ref.)

MYOCARDIAL DISEASES, SECONDARY

Cardiomyopathy associated with systemic diseases. Wheeler R, et al.
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MYOCARDIAL INFARCT

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Nutritional therapy in acute myocardial infarction. Christakis G, et al.
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NOREPINEPHRINE

Adrenergic, cholecystokinetic and morphine-induced effects on extra-hepatic biliary motility. Persson CG.
Acta Physiol Scand [Suppl] 383:1-32, 1972 (108 ref.)

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Pericarditis and pericardial effusion. Radiologic and echocardiographic diagnosis. Ellis K, et al.
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Circulatory reflexes from mechanoreceptors in the cardio-aortic area. Pelletier CL, et al.
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Prostaglandin E1 and platelets. Bousser MG.
Biomedicine 18:95-102, Mar 73 (63 ref.)

Hypertension and human renal prostaglandins. Vance VK, et al. **Med Ann DC 42:419-22, Sep 73 (31 ref.)**
Hypertension, natriuresis and the renomedullary prostaglandins: an overview. Lee JB.
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Renomedullary interstitial cells (RIC), prostaglandins (PG) and the antihypertensive function of the kidney. Muirhead EE, et al.
Prostaglandins 3:581-94, May 73 (30 ref.)

PULMONARY ARTERY

Pulmonary arteriovenous fistulas in children. A review with special reference to the disperse telangiectatic type, illustrated by report of a case. Utzon F, et al.
Acta Paediatr Scand 62:422-32, Jul 73 (36 ref.)

PULMONARY HEART DISEASE

Cardiovascular complications of chronic bronchitis and emphysema. Bishop JM.
Med Clin North Am 57:771-80, May 73 (37 ref.)

PULMONARY VEINS

Pulmonary arteriovenous fistulas in children. A review with special reference to the disperse telangiectatic type, illustrated by report of a case. Utzon F, et al.
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RAYNAUD'S DISEASE

If your patient can't tolerate the cold--suspect cryoglobulinemia. Costanzi JJ, et al.
Med Times 100:55-63, Sep 72

SHOCK

Current therapy of shock. Goldberg LI, et al.
Adv Intern Med 17:363-78, 1971 (96 ref.)

SHOCK, ENDOTOXIC

Acute renal failure in obstetric septic shock. Current views on pathogenesis and management. Emmanouel DS, et al.
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TACHYCARDIA

Rapid atrial stimulation in the treatment of supraventricular tachycardia. Lister JW, et al.
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TELANGIECTASIS

Pulmonary arteriovenous fistulas in children. A review with special reference to the disperse telangiectatic type, illustrated by report of a case. Utzon F, et al.
Acta Paediatr Scand 62:422-32, Jul 73 (36 ref.)

THROMBOPHLEBITIS

Recent advances in venous thrombo-embolism. A review article. Sobel JD.
S Afr Med J 47:1197-202, 14 Jul 73 (53 ref.)

VASCULAR DISEASES

Microcirculation and metabolism in the vascular wall concerned with the vasa vasorum. Nakata Y, et al.
Jap Circ J 37:217-27, Mar 73 (28 ref.)

VASODILATOR AGENTS

Labyrinthine vasodilators. Snow JB Jr, et al.
Arch Otolaryngol 97:365-70, May 73 (28 ref.)

VASOMOTOR SYSTEM

Vascular reactivity in systemic arterial hypertension. Mendlowitz M. **Am Heart J 85:252-9, Feb 73 (70 ref.)**

VENTRICULAR FIBRILLATION

Anodal stimulation as a cause of pacemaker-induced ventricular fibrillation. Preston TA.
Am Heart J 86:366-72, Sep 73 (80 ref.)

BOOK REVIEWS

CEREBRAL VASCULAR DISEASES, 8th Conference, January 5–7, 1972, edited by F. H. McDowell and R. W. Brennan. New York, Grune & Stratton, 1973, 319 pages

As in the previous volumes of this series which began in 1954, the latest developments in the field of cerebrovascular diseases are presented. Again there are the discussions in full, and the opportunity to compare diametrically opposed conclusions from the same data. That sacred cow of medicine, the cooperative study (in this case "Joint Study of Extracranial Cerebrovascular Disease") is treated as anything but holy by several critics deploring its methods, its conclusions and its cost. Unfortunately, some discussants tend to substitute personal, unsupported opinions for the conclusions they attack. To summarize the results of the Joint Study to date: they are inconclusive and indicate only that surgery is or is not of value in the treatment of cerebral vascular lesions.

Basic research on cerebral metabolism in ischemia and some refined angiographic techniques are well presented. The gamma camera (for those who can afford it) promises to give valuable information about cerebral blood flow. The diagnosis of carotid arterial stenosis can often by made by this noninvasive method.

Four reports present the effect on cerebrovascular disease of certain drugs (chiefly aspirin and sulfinpyrazone) that reduce the adhesive and cohesive properties of platelets. As presented here (and in some subsequent reports) this work looks promising clinically—the statistics equaling those for surgery. However, there have already been two large series (referred to here but not part of the conference) in which use of these agents produced no benefit.

An article entitled "Clinical Management of Cerebral Ischemia" describes several treatments for acute stroke that the authors claim are "of value," although the evidence did not impress this reviewer and failed to convince two discussants with comparable experience in the specific methods cited.

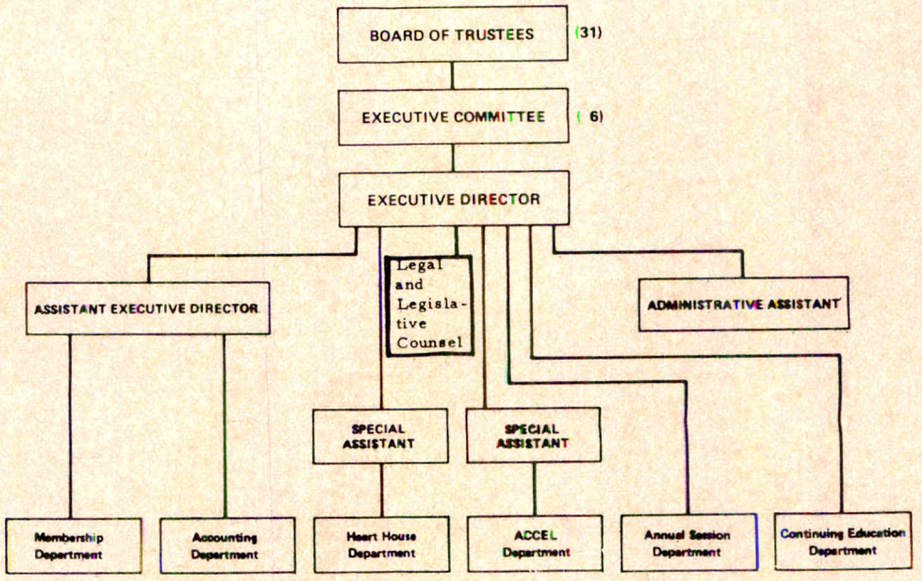
In summary, this volume documents the sad fact that we have gone another 12 months without a real breakthrough in this important but depressing medical field.

Philip S. Bergman, MD
New York, N.Y.

Report To:

The Executive Committee and The Board of Trustees

American College of Cardiology: Table of Organization



Since my last report to you, there have been several administrative changes which I have effected in our table of organization. These additions to our professional "management team" have resulted in a better distribution of work responsibilities in the American College of Cardiology Central Office and hopefully we are now in a better position to respond quickly to the needs of the Board of Trustees, committees and indeed the entire membership of the College.

It has been apparent to me for almost a year that finding an Assistant Executive Director of the College was a must. We were fortunate in attracting a most qualified professional to fill this position. Dwight Monnier joined the staff in the late summer and has brought to us many talents. He had served as Vice President of American University in Beirut for seven years.

Our HEART HOUSE Planning and Development Department is headed by Theodore G. Kummer who came with us this past summer. Ted has good credentials in the professional society management field as well as considerable background in the audio-visual field.

Albert S. Pasini, another important segment of our management team, directs the expanding ACCEL programs. In addition, in his role as Special Assistant to the Executive Director, he staffs several of our key committees and is assisting with HEART HOUSE planning needs.

The part-time Legislative Counsel in the person of Mr. Raymond D. Cotton has given us the help we sorely needed in this area. He is available at all times for advice and his contacts, both in Congress and within the federal agencies, are invaluable.

The part-time assistance of a professional health writer with our CARDIOLOGY Newsletter is essential, and I am grateful to you for the Newsletter budget which permits this assistance.

I cannot commend too highly the work of all individuals on our 25–30 person staff. They are interested, enthusiastic and totally devoted to assisting you in every way. We all consider it a privilege to work for the College. The time which each of you devote as volunteers to College activities is most appreciated.

This past year has seen a healthy growth in the College. We continue to add quality to our membership roles. With the raise in dues in January 1973 we are able to keep our finances in the black. The Leadership Conferences this past summer afforded another excellent opportunity for communication between the officers and staff of the College and the membership across the nation. I would strongly recommend that these be repeated in 1974. The Governors are asking long overdue questions about their real role in College activities. Hopefully this dialogue will result in a more meaningful role for the College Governors.

Planning for HEART HOUSE is taking a tremendous amount of staff time and Building Facilities Committee time. It is needed and will be well worth the effort. If we are not immediately available to answer your question about some matter, please have patience with us. We'll respond as rapidly as humanly possible.

And finally, I appreciate the time which the officers have granted to me to serve as President of the Professional Convention Management Association during 1974. The duties will not take me away from Bethesda very often and I hope that my tenure as President will reflect credit to the American College of Cardiology.

WILLIAM D. NELLIGAN
Executive Director
American College of Cardiology

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

JAN. 10–12 — **Non-Invasive Methods in Cardiac Diagnosis.** Ernest Craige, FACC, director. University of North Carolina School of Medicine, Chapel Hill N. C.

JAN. 11–13 — **Core Curriculum: Cardiovascular Physiology: Clinical Utilization of Invasive and Non-Invasive Measurements.** William W. Parmley, FACC, James S. Forrester and H. J. C. Swan, FACC, directors. Riviera Hotel and Country Club, Palm Springs, Calif.

JAN. 13–15 — **The Cardiac Care Unit in 1974—Integrated Medical-Surgical Care in Acute Coronary Artery Disease.** John H. K. Vogel, FACC, director. Opticon Theater, Snowmass at Aspen, Aspen, Colo.

FEB. 11–14 — **Twenty-third Annual Scientific Session.** H. J. C. Swan, FACC, president. Americana Hotel and New York Hilton, New York, N. Y.

FEB. 15–17 — **1974 Reconvened Annual Scientific Session.** Carlos E. Bertran, FACC, director. Hyatt Hotel, San Juan, P. R.

MAR. 18–22 — **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Mt. Sinai Medical Center, New York, N. Y.

MAR. 21–23 — **Core Curriculum: Pathology of the Heart.** Maurice Lev, FACC, director. Palmer House, Chicago, Ill.

MAR. 25–27 — **Electrocardiographic Interpretation of Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis.

MAR. 28–30 — **High Blood Pressure—When and How To.** Robert S. Eliot, FACC, director. Gerald L. Wolf and Francis L. Land, co-directors. University of Nebraska Center for Continuing Education, Omaha, Nebr.

APR. 1–10 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 4–6 — **Advances in Clinical Cardiology.** Lawrence S. Cohen, FACC, director. Yale University School of Medicine, New Haven, Conn.

APR. 17–19 — **Core Curriculum—Vectorcardiography (A Basic Workshop).** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

APR. 22–25 — **Current Concepts in Cardiology—1974.** Philip R. Akre, director. Grand Hotel, Las Vegas, Nev.

MAY 6–9 — **The Treatment of Coronary Syndromes.** J. Willis Hurst, FACC, director. Royal Coach Motor Hotel, Atlanta.

MAY 9–11 — **The Ventricular Ectopic Beat: Heart-throb or Harbinger of Death.** Bernard Tabatznik, director. Urban Life Center, Columbia, Md.

MAY 15–17 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director. Georgetown University School of Medicine, Washington, D. C.

MAY 17–19 — **Core Curriculum: Rational Drug Therapy in Cardiovascular Disease.** Robert J. Lee, PhD., director. The Nassau Inn, Princeton, N. J.

MAY 23–25 — **Cardiologist's Appraisal of Operable Heart Disease.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. St. Francis Hotel, San Francisco, Calif.

JUNE 6–8 — **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director. Town and Country Hotel, San Diego, Calif.

Membership in the American College of Cardiology

The American College of Cardiology membership includes physicians and scientists working together to promote the continuing education of physicians concerned with cardiovascular disease. Its single purpose is to encourage the development of learning experiences designed to update knowledge and clinical behavior of physicians, surgeons and scientists, thereby promoting high quality health care delivery through application of new information.

The College attempts to accomplish this objective through a balanced array of programs including the *Annual Scientific Session,* consisting of reports of original research, lectures, core curricula, panel discussions, clinical demonstrations, small seminars with master teachers, films, self-assessment testing and scientific and technical exhibits; some 30 *regional scientific seminars* of 1 to 10 days' duration; the official monthly publication of the College, *The American Journal of Cardiology; ACCEL,* a multi-media journal which features a monthly audio cassette tape; *International Circuit Courses* (co-sponsored by the U. S. Department of State) presenting up-to-date information on cardiovascular disease to medical communities in foreign countries; and special *Bethesda Conferences* designed to encourage the exchange of ideas on policies concerning the practice of cardiology and matters affecting service, investigation and training relative to cardiovascular disease.

Membership in the College provides several direct advantages relating to the above objective: subscription to *The American Journal of Cardiology,* waiver of the registration fee for attendance at the annual scientific session, reduced fees for attendance at regional continuing education programs, reduced subscription rate for *ACCEL,* and receipt of *Cardiology.*

The College has three categories of membership: Fellowship, Associate Fellowship and Affiliate. Fellowship acknowledges that the individual has achieved a significant degree of professional maturity in cardiology, and that his primary medical interest is the prevention and treatment of this disease. Accordingly, election to Fellowship is recognition of achievement, not of promise. Depending upon such factors as training, acknowledgment of abilities by peers, and age, individuals are elected to membership at the Associate Fellowship or Affiliate level. Election to Associate Fellowship recognizes those individuals who have completed formal training in cardiology and are qualified for the subspecialty boards; the category of Affiliate recognizes younger individuals who exhibit an interest in cardiology by participation in a cardiology training program, as well as older individuals whose practice is predominately cardiology but who have had limited formal specialty training.

The future strength and health of the organization is largely dependent upon the quality of the young cardiologists, cardiac surgeons, cardiovascular radiologists and basic scientists who become participating members. Therefore, we encourage membership for those individuals still in training programs and hope for their active interest in College affairs.

Further information on the procedure for making application to the College can be obtained by writing Mrs. Nancy A. Bish, director, Membership Department, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

DONALD C. HARRISON, MD, FACC
Chairman, Membership Committee

Candidates Certified

Candidates Certified by Subspecialty Board on Cardiovascular Disease January through June 1973

Algary, William P., MD
Greenville, South Carolina

Allan, Mary B., MD
Westtown, Pennsylvania

Allen, John W., MD
Hacienda Heights, California

Al-Sadir, Jafar M., MD
Chicago, Illinois

Anderson, Robert F., MD
Austin, Texas

Bashour, Tali T., MD
West Hyattsville, Maryland

Becker, Lewis C., MD
Chapel Hill, North Carolina

Beckwith, William R., MD
Haverford, Pennsylvania

Beeson, Charles W., II, MD
Savannah, Georgia

Bemis, Charles E., MD
San Diego, California

Berberich, Stephen N., MD
Marblehead, Massachusetts

Beregovich, Jonas, MD
New York, New York

Black, Henry E., MD
Buffalo, New York

Block, Paul J., MD
Long Branch, New Jersey

Bloomfield, Martin E., MD
New York, New York

Bost, Charles R., MD
Keesler AFB, Mississippi

Bures, Alan R., MD
Irvine, California

Burwell, Lawrence R., MD
Rochester, New York

Capone, Robert J., MD
Barrington, Rhode Island

Cashion, William R., Jr., MD
O'Fallon, Illinois

Chaithiraphan, Suphachai, MD
New York, New York

Clark, Dwight W., Jr., MD
Atlanta, Georgia

Cochran, Paul T., MD
Albuquerque, New Mexico

Cohen, Martin N., MD
Port Chester, New York

Cole, James S., MD
Houston, Texas

Corcoran, Francis H., MD
Potomac, Maryland

Costantino, Thomas, MD
Staten Island, New York

Coyne, James J., MD
Maplewood, New Jersey

Crawley, Ina S., MD
Decatur, Georgia

Crews, Thomas L., MD
Covington, Georgia

Cundey, David W., MD
Augusta, Georgia

Dalen, James E., MD
Chestnut Hill, Massachusetts

Danzig, Ronald, MD
Sherman Oaks, California

Davidson, Robert M., MD
Camp Springs, Maryland

Davis, Robert J., MD
Rochester, New York

Diaco, Nicholas V., MD
Los Angeles, California

Dickhaus, Donald W., MD
Columbia, Missouri

Dietz, Richard F., Jr., MD
Falls Church, Virginia

Draur, Ronald A., MD
Omaha, Nebraska

Eckberg, Dwain L., MD
Iowa City, Iowa

Edelstein, Stephen G., MD
Lexington, Kentucky

Epstein, Peter J., MD
Bayside, New York

Eubanks, Donald R., MD
Memphis, Tennessee

Falcone, Michael W., MD
Sheppard Air Force Base, Texas

Farr, David, MD
Northport, New York

Finney, James O., Jr., MD
Keesler Air Force Base, Mississippi

Fleming, Timothy, MD
Lander, Wyoming

Forker, Alan D., MD
Lincoln, Nebraska

Fortuin, Nicholas J., MD
Baltimore, Maryland

Gallagher, Hugh S., MD
Allentown, Pennsylvania

Gambetta, Miguel, MD
Chicago, Illinois

Geraci, Anthony R., MD
Toledo, Ohio

Gilbert, Charles A., MD
Atlanta, Georgia

Goldfinger, Paul, MD
Virginia Beach, Virginia

Goodman, Mark Alan, MD
Pensacola, Florida

Gough, David C., MD
APO New York, New York

Goulden, Dudley D., III, MD
San Antonio, Texas

Grais, Ira M., MD
Lincolnwood, Illinois

Green, John G., MD
Havre de Grace, Maryland

Gross, Howard E., MD
Orlando, Florida

Groves, Bertron M., MD
Tucson, Arizona

Guiney, Timothy E., MD
Boston, Massachusetts

Hallal, F. Joseph, MD
Washington, D. C.

Hammermeister, Karl E., MD
Bellevue, Washington

Hansing, Charles E., MD
Bellevue, Washington

Harbold, Norris B., Jr., MD
Charlotte, North Carolina

Harrison, Frank S., Jr., MD
Gladwyne, Pennsylvania

Hawkins, Henry M., Jr., MD
Tulsa, Oklahoma

Higgins, Thomas G., MD
South Orange, New Jersey

Hill, John C., MD
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Holmsten, R. David, MD
Muskogee, Oklahoma

Horwitz, Lawrence D., MD
Dallas, Texas

Hynes, Kieran M., MD
Dayton, Ohio

Itscoitz, Samuel B., MD
Bethesda, Maryland

Iyengar, Ramanuja N. V., MD
Miami Beach, Florida

Jacobson, Lester B., MD
San Francisco, California

Jensen, Jay B., MD
Lubbock, Texas

Johnson, Allen D., MD
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Johnson, Lewis W., Jr., MD
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Joines, Iverson W., II, MD
Decatur, Georgia

Jonas, Ernesto A., MD
Chestnut Hill, Massachusetts

Katz, Donald I., MD
Ramapo, New York

Keller, Wayne W., MD
Gladwyne, Pennsylvania

Kerber, Richard E., MD
Iowa City, Iowa

Keroes, Jonathan, MD
San Francisco, California

King, Alan S., MD
Albuquerque, New Mexico

Knope, Russell F., MD
Fayetteville, New York

Kotler, Morris N., MD
Villanova, Pennsylvania

Landesman, Richard H., MD
Highland Park, Illinois

Leaman, David M., MD
Hershey, Pennsylvania

Lee, Dixon A., MD
Rockville, Maryland

Leshin, Stephen J., MD
Dallas, Texas

Levit, Simon A., MD
Tulsa, Oklahoma

Linhart, Joseph W., MD
Paoli, Pennsylvania

Lipscomb, Kirk M., MD
Seattle, Washington

Littleford, Philip O., MD
Orlando, Florida

Lufschanowski, Roberto, MD
Houston, Texas

Manchester, Joel H., MD
Philadelphia, Pennsylvania

Marcus, Melvin L., MD
Willingboro, New Jersey

Margolis, S. Eugene, MD
Woodland Hills, California

Mark, Allyn L., MD
Iowa City, Iowa

Massin, Edward K., MD
Houston, Texas

Mateo-Torres, Fermin, MD
Dos Pinos, Rio Piedras, Puerto Rico

Matthews, Minor E., MD
Medford, Oregon

Matthews, Oscar A., MD
Huntington Beach, California

McBride, John W., MD
St. Paul, Minnesota

McCarron, William E., MD
Austin, Texas

McDonald, Charles D., Jr., MD
Chattanooga, Tennessee

Medina, Jose R., MD
Tulsa, Oklahoma

Merrill, Arthur J., Jr., MD
San Antonio, Texas

Mookherjee, Saktipada, MD
Syracuse, New York

Morgan, John F., MD
Villa Park, Illinois

Morse, John R., MD
San Diego, California

Munir, Muhammad, MD
Pottsville, Pennsylvania

Murgo, Joseph P., MD
San Antonio, Texas

Nachnani, Gurbux H., MD
Alexandria, Virginia

Natarajan, Ponnuswamy, MD
Medford, Massachusetts

Nemickas, Rimgaudas, MD
Riverside, Illinois

Obeid, Anis I., MD
Syracuse, New York

Oboler, Allen A., MD
Washington, D. C.

O'Donoghue, John K., MD
River Forest, Illinois

Page, Edward E., MD
Jacksonville, Florida

Palay, Howard J., MD
Green Bay, Wisconsin

Patterson, Jack A., MD
Belleville, Illinois

Patton, Robert M., MD
New Orleans, Louisiana

Pekaar, Robert L., MD
Augusta, Georgia

Pepine, Carl J., MD
Cherry Hill, New Jersey

Phillips, Daniel F., MD
Cleveland, Ohio

Pinkernell, Bruce H., MD
New York, New York

Pomerantz, Barry, MD
Spring Valley, New York

Pool, Peter E., MD
Solano Beach, California

Ramirez, Alberto, MD
Boston, Massachusetts

Rater, David A., MD
Cedar Rapids, Iowa

Reddy, Sudhakar P., MD
Pittsburgh, Pennsylvania

Regnante, Richard M., MD
North Easton, Massachusetts

Riley, Charles P., MD
Pensacola, Florida

Robinhold, Daniel G., III, MD
Eugene, Oregon

Robinson, Norman J., MD
Wilmington, North Carolina

Rotman, Michael, MD
San Antonio, Texas

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Rubenfire, Melvyn, MD
Detroit, Michigan

Rubenstein, Joel J., MD
Natick, Massachusetts

Russell, Thomas, II, MD
Cannon AFB, New Mexico

Russo, John V., MD
Kensington, Maryland

Santer, Michael A., Jr., MD
Parkersburg, West Virginia

Sarche, Michael A., MD
USAF Academy, Colorado

Saunders, Wade H., III, MD
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Mill Valley, California

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Silvers, Norman P., MD
Cherry Hill, New Jersey

Silverstein, H. Robert, MD
Hartford, Connecticut

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Stone, John M., MD
Berkley, Michigan

Strauss, George S., MD
Marshfield, Wisconsin

Sullivan, Robert W., MD
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Teng, Cheng Yee, MD
Darien, Illinois

Thompson, Mark E., MD
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Towne, William D., MD
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Vincent, G. Michael, MD
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Evanston, Illinois

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Zitnik, Ralph S., MD
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Sub-Board of Pediatric Cardiology
October 1973

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Durham, North Carolina

Arnon, Rica G.
Forest Hills, New York

Bessinger, Forrest Blanton, Jr.
Minneapolis Minnesota

Chiemmongkoltip, Pipit
Skokie, Illinois

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Vestal, New York

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Welcome to New York City in February

You are cordially invited to attend the 23rd Annual Scientific Session of the American College of Cardiology in New York City, to be held on February 11–14, 1974. It is particularly appropriate to hold this 25th anniversary meeting in New York City because the College was founded here in 1949. The founders and New York members will do their utmost to make this meeting an outstanding event.

New York City is an exciting place to hold a College meeting. The attractive New York Hilton and Americana Hotels, located across the street from each other, will house most of the registrants. The technical and scientific exhibits, scientific sessions, fireside conferences, luncheon panels and all other ancillary programs will be held in the meeting rooms of these two hotels. They are conveniently located close to all amusement, educational and business centers of our city.

The scientific sessions, organized by Eliot Corday and his Scientific Program Committee, are oriented for the clinical cardiologist. They will be preceded by the popular Cardiac Clinics which are sponsored by the divisions of cardiology of seven metropolitan medical schools and their affiliated teaching hospitals. The faculty includes teachers, clinicians and investigators in the forefront of cardiology in the New York area who will review advances and current problems in clinical diagnosis and medical and surgical treatment of heart disease, by the use of lectures, patient demonstrations and graphic methods.

The Cardiac Clinics begin at 9 AM on Monday, February 11. Buses will pick up the registrants at 8 AM. Please try to check into your hotel on Saturday or Sunday, February 9 or 10 and preregister for the Cardiac Clinics with your advance registration form, or on arrival at your hotel.

The various convention committees and the Ladies Entertainment Committee will do their best to make the New York meeting a pleasant, exciting and educational experience.

Simon Dack, MD, FACC
General Chairman

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is pleased to offer you and a member
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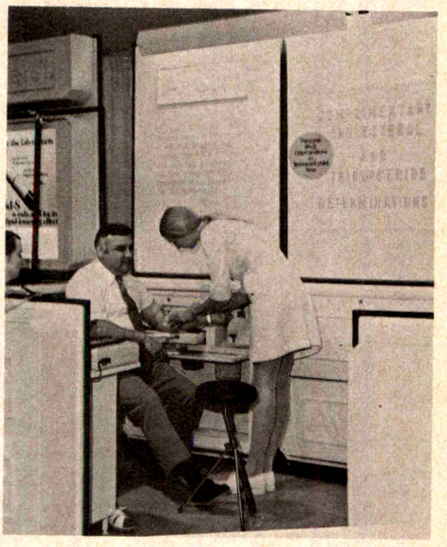

The 12-14 hour fasting blood samples†
will be drawn at the Ayerst exhibit
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New York, N. Y.
February 11-14, 1974

BOOTHS NO'S. 371 AND 372	BOOTH NO. 103
at the New York Hilton Hotel	**at the Americana Hotel**

*Serum cholesterol and triglyceride determinations.
†No eating or drinking after early dinner the evening before.

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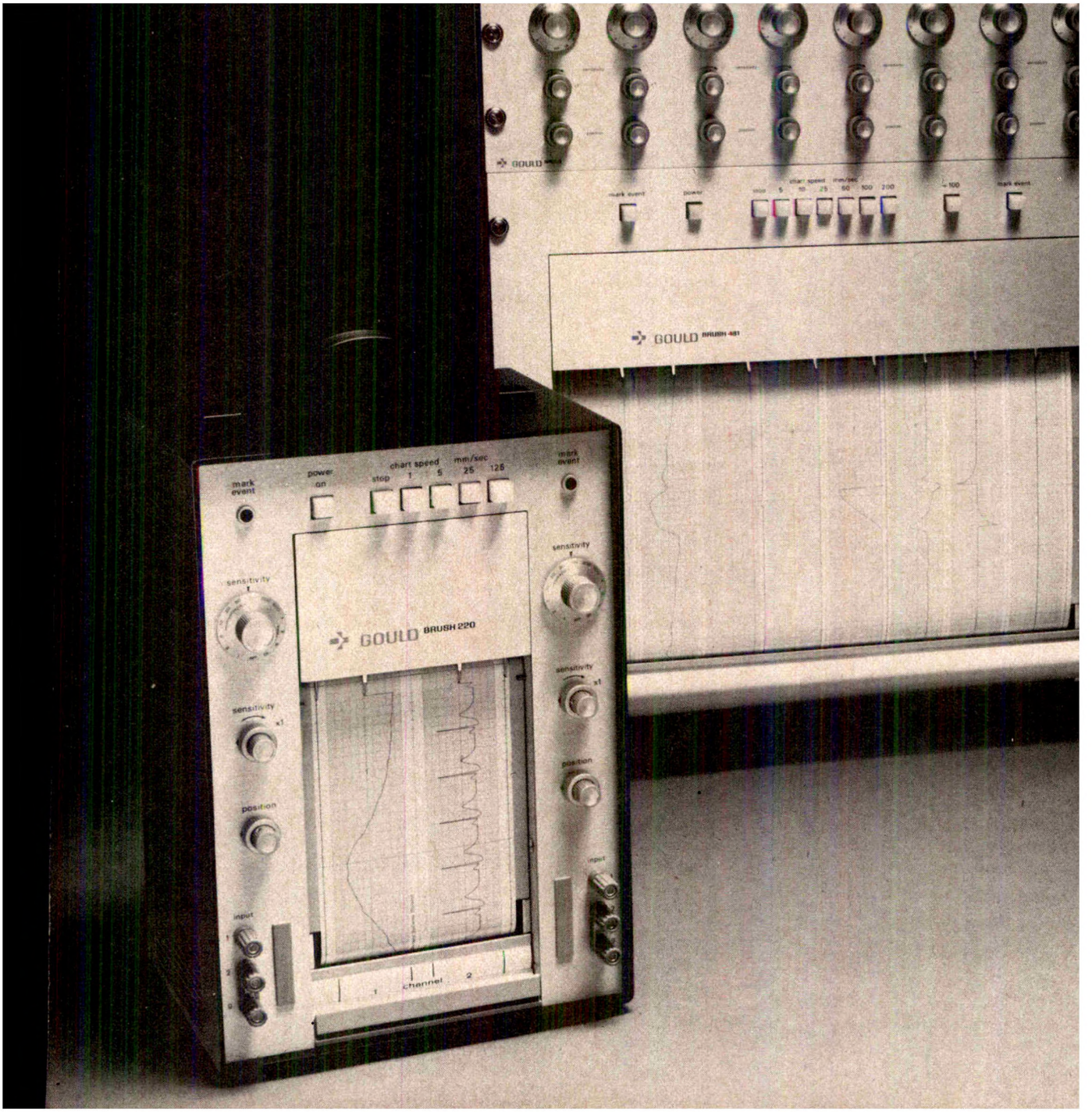
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Brush traces are the standard of the industry. Our pressurized inking system eliminates smudges, smears, skips and puddles because the traces are actually forced into the paper. The record you get is crisp, clear and permanent.

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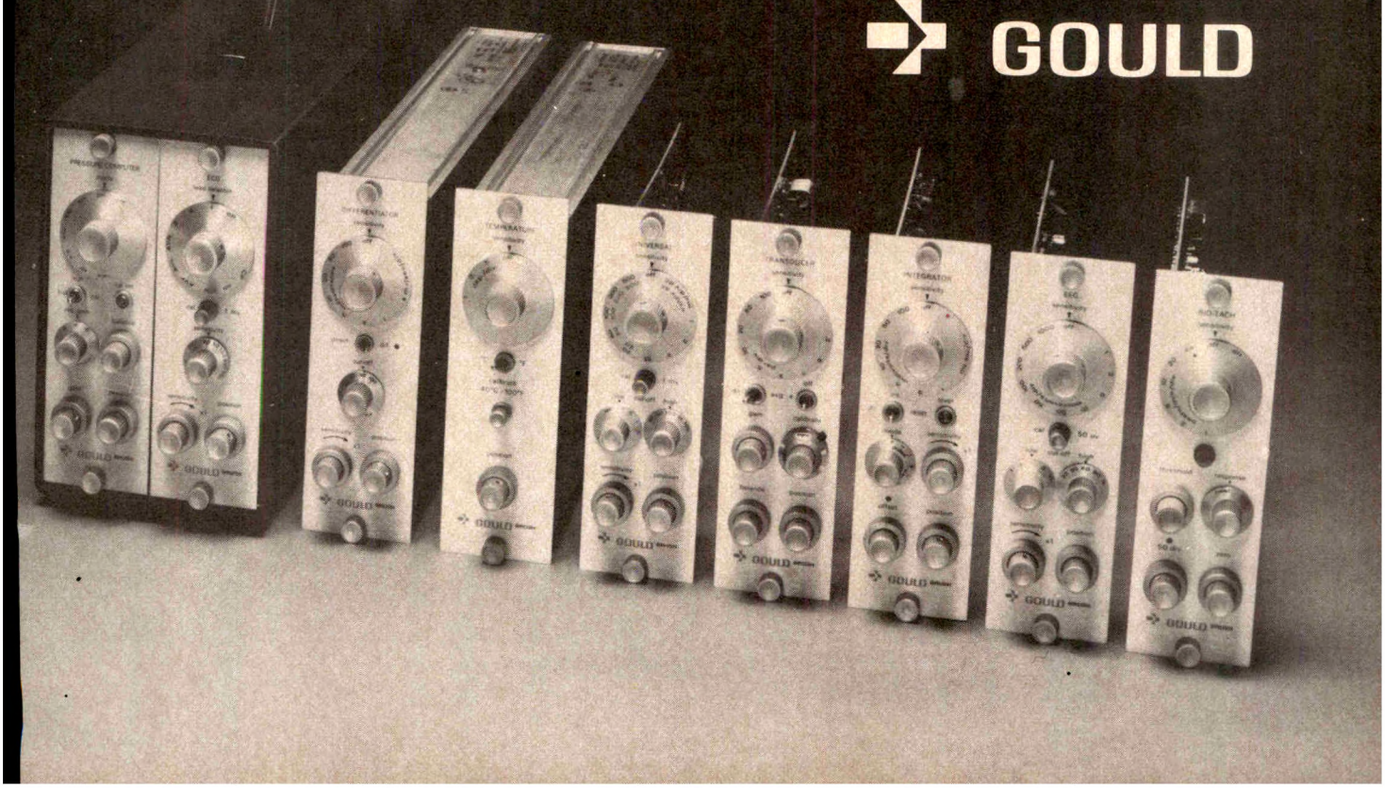


System 80.

The Second Generation Intra-Aortic Balloon Pump. It Has The Gas, The Balloon, And The Logic.

The Datascope System 80. Our system for Intra-Aortic Balloon Pumping. It uses CO_2 to pump the intra-aortic balloon. Not Helium. And because the intra-aortic balloon connects to a slave balloon in a Safety Chamber, the gas system is closed. Not open. Which means only a fixed volume of CO_2 is transferred from one balloon to another.

Our intra-aortic balloon* is unique. The Dual-Chamber Intra-Aortic Balloon. It pumps blood preferentially towards the heart during balloon inflation. Experimental data[1] show an average increase of 66-100% in coronary blood flow over and above that obtained with a single-chamber balloon.

Our system also offers you superior pumping logic. Complementary Pulse Logic. Something like turning a lamp off first instead of on. The R-wave triggers *deflation* of the balloon at the onset of systole following *that* R-wave; inflation follows systole and automatically adjusts itself for the duration of diastole. Which means our system tracks irregular rhythms.

Our system is also complete. Modular and Mobile. With Battery-powered, synchronized** monitoring of ECG and aortic pressure. And optional battery-pack for pumping without external power.

Call us at area code 201-845-7650. Or write to Datascope Corporation, 520 Victor Street, Saddle Brook, New Jersey 07662. We'll be happy to send you reprints of published clinical experience with our system, information on clinical evaluation and experimental studies now in progress and a Guidebook to Intra-Aortic Balloon Pumping which describes System 80 in detail.

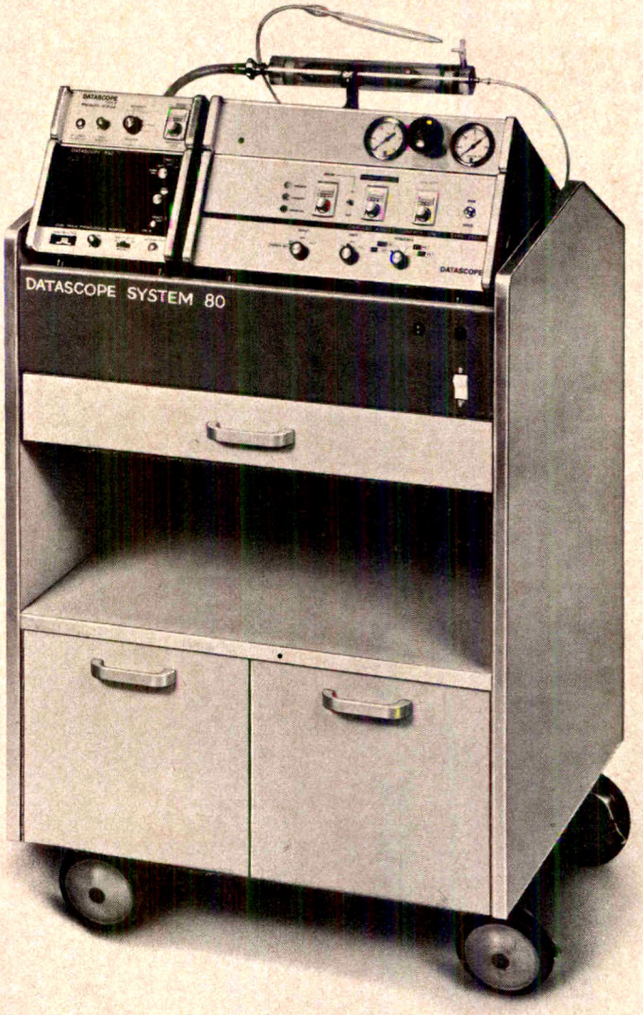
Besides Intra-Aortic Balloon Pumping, we might also mention that our system will perform in a variety of pneumatically powered procedures for assisted circulation. That's logical too.

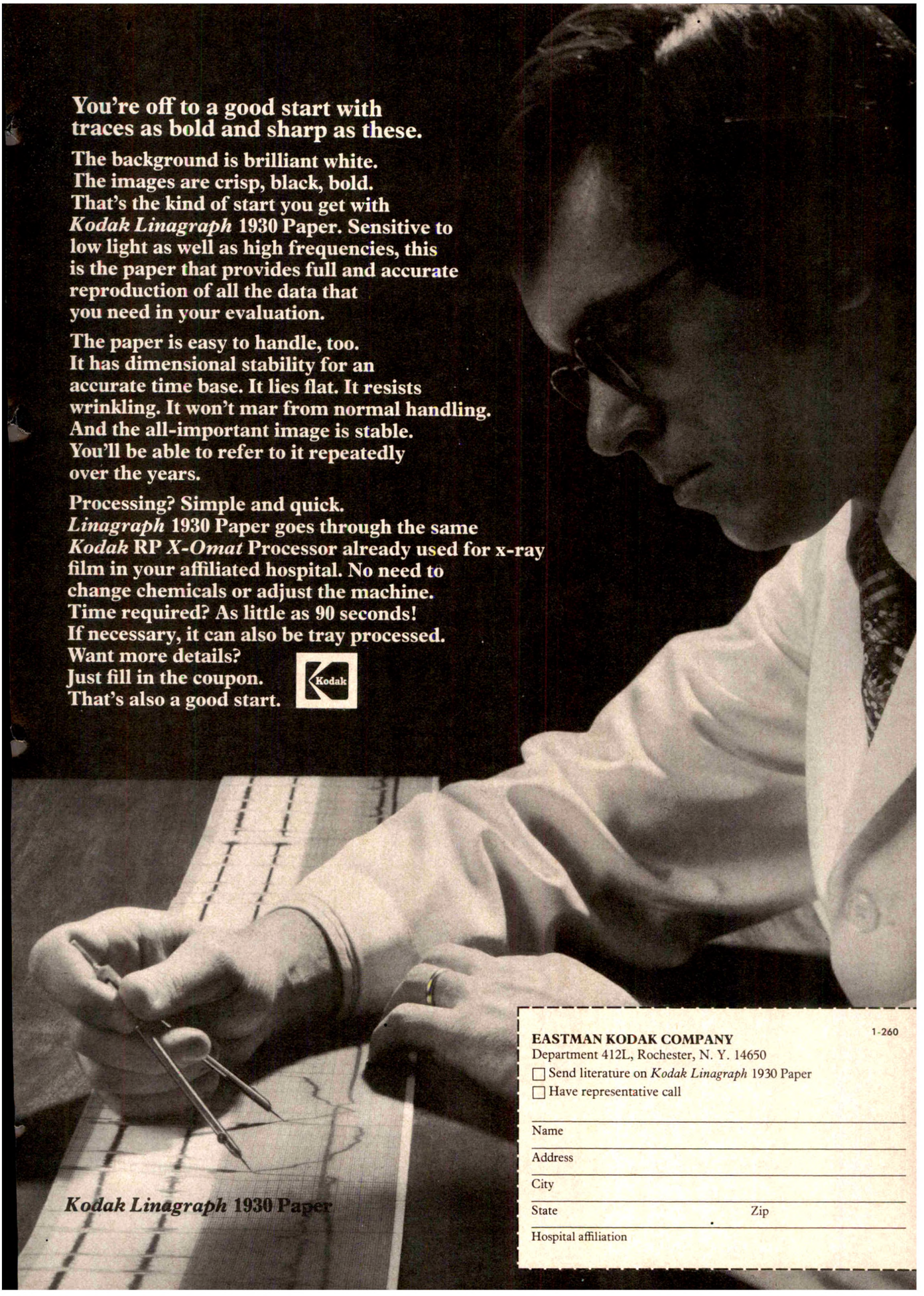
*patent pending

1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

**U.S. Patent #3,347,452

Datascope System 80





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Rheumatic fever prevention.
Here's true convenience for patients who must receive prophylactic penicillin indefinitely. A prolonged-action penicillin—benzathine penicillin G. Recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. A single monthly injection (1,200,000 units) offers continuous prophylaxis in most patients.

Action against strep.
In therapy of mild to moderate group A streptococcal pharyngitis (without bacteremia), prolonged action again commends this penicillin, named by authorities a method of choice.* Just one injection (600,000 to 900,000 units in children and 1,200,000 units in adults) usually maintains serum concentrations for the ten days considered necessary to eradicate the streptococci and preclude the initial onset of rheumatic fever.†

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.
The following infections usually respond to adequate dosage of IM benzathine penicillin G.
Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).
Venereal infections—Syphilis, yaws, bejel, and pinta.
Medical Conditions in which Benzathine Penicillin G Therapy is indicated as Prophylaxis:
Rheumatic fever and/or chorea—Prophylaxis with benzathine penicillin G has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.
Contraindications: Previous hypersensitivity reaction to any penicillin.
Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.
Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.
Carefully avoid intravenous or intraarterial use or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.
†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.
Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures if superinfection occurs.
Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.
As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.
Composition: (units benzathine penicillin G as active ingredient): 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.
600,000 units in 1-cc. TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.
1,200,000 units in 2-cc. TUBEX, packages of 10, and in 2-cc. single-dose disposable syringe.
2,400,000 units in 4-cc. single-dose disposable syringe.
Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben.

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Month-long rheumatic fever prophylaxis gives freedom from daily dosage.

Make Life Easier For You And Your Pacer Patients

Now, with the advent of the ESB Medcor Pacer-Check* system, it is possible for your office to conduct regular, accurate recordings of heart pacer patient's ECG and pacer rates by telephone.

Both you and your patients benefit. Now, with no more than a phone call, you can have information which permits elective decisions on replacement rather than emergency or prophylactic replacements. (By using a regular patient checking program, maximum pacer life can be realized.) Your patient and you have flexibility and safety at the same time.

This two-component system operates simply, requiring minimal training to both your personnel and patients.

The Medic Unit, at left, is the central component and is usually located in the hospital or clinic. It receives ECG and pacer rate input via unaltered telephones from the Patient Unit which is usually located in the patient's home. ECG data, produced on a standard paper chart, indicates the relationship between the QRS complex and pacer artifact to ascertain pacer capture. Pacer rate is shown continuously by illuminated numbers on the front panel. This is the first system available to physicians that records ECG and simultaneously displays pacer rate.

The Patient Unit is lightweight and battery powered. It is capable of transmitting from any telephone to your office. Transmissions have been successfully made from such great distances as Tokyo to New York. To operate, the patient places the telephone headset in the receiving cradle and then slips the two expandable bracelets over his forearms. Transmission begins immediately.

The Pacer-Check* system, approved for reimbursement by Medicare, has proven itself a useful and self-supporting method of maintaining a desirable pacer program.

If the unique qualities of the Pacer-Check* system interest you, contact ESB Medcor, Inc., Dept. 373, 5920 Rodman St., Hollywood, Florida 33023. Toll free call: (800) 327-9780, Ext. 373.

ESB Medcor™

Sentry 75
ventricular inhibited pulse generator

GENERAL ELECTRIC

Sentry 75... one generator that meets long-term pacing demands

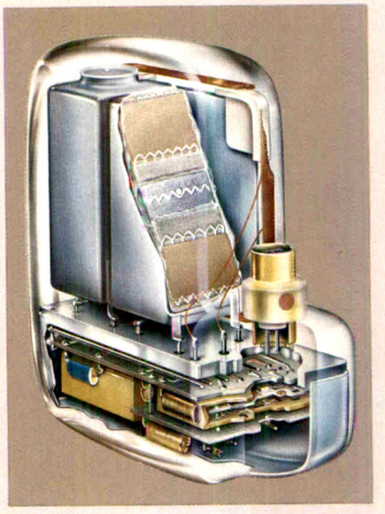
The Sentry 75 ventricular inhibited pulse generator maximizes the potentials of a proven power source to deliver extended pacing life to most patients, regardless of threshold value.

It is General Electric's positive response to the medical profession's demand for a simple, extended-life pacing system to serve the large majority of patients.

The Sentry 75 presents no alterations in implant technique or patient management. It is compatible with all GE electrodes, and the long reliable service life can be monitored easily by both patient and physican.
The Sentry 75 is powered by the industry's first mercury/zinc cells specifically designed for implantable pulse generator applications. A complete redesign of both this power cell and circuitry now make possible a pulse generator which can be expected to deliver a 4 to 6 year life, with an assurance factor greater than generators using normal mercury/zinc batteries.

Your GE representative can provide you with information regarding patient testing, warranties, and availability in your area.

Optimized power source capability.



Redesigned power cells. The mercury/zinc battery is a long proven power source familiar to the medical profession. Its chief liability has not been in the chemical composition, but in its construction. GE design aims were to maximize power utilization and reduce internal losses to produce a power cell capable of far longer and more reliable service life.

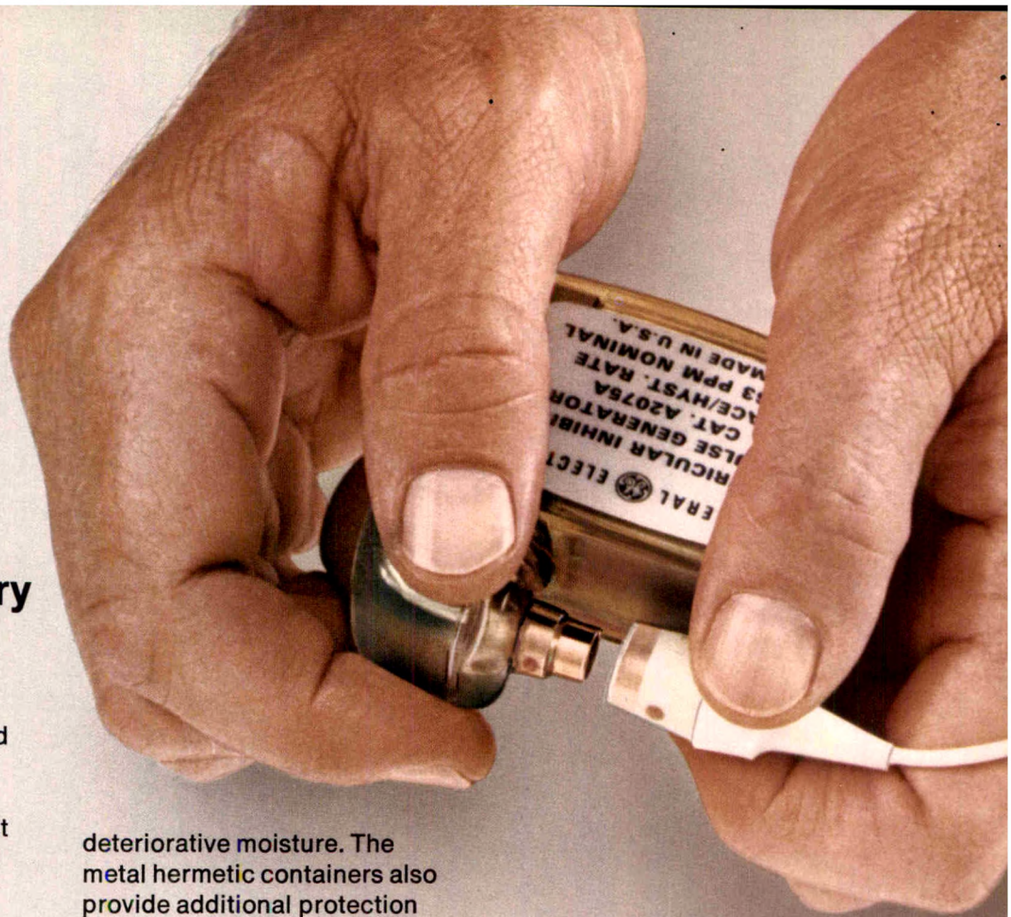
Note the new GE power cell is rectangular. It displaces the same volume as 2 circular batteries, yet contains 50% greater capacity (3000 mA hours vs. 2000) than 2 circular batteries operating in parallel. Two of these high-capacity cells, connected in series, power the pulse generator.

Internal discharge, a problem with previous batteries resulting from shorting electrodes, has been virtually eliminated by 6 wraps of a new non-degradeable separator. These multi-wraps replace the single-wrap separator presently used in mercury/zinc batteries.

The power cell case is solid nickel to prevent case-to-electrolyte reaction, another potential source of self-discharge.

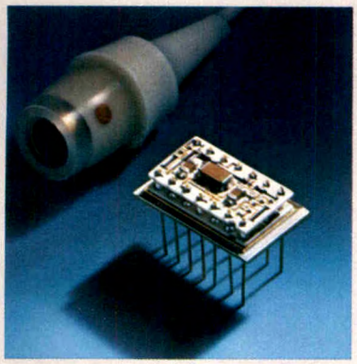
Welded internal contacts to electrodes preclude the possibility of "open" contacts, a design shortcoming with ordinary pressure contacts.

The negative terminal is isolated from the cap through a hermetic ceramic-to-metal seal, and the cap is welded to the top of the cell to prevent electrolyte seepage across the 2 terminals. And as one last safety precaution, the positive pressure vent is located at the end of the cell, remote from the terminals.



Simplified circuitry for reliability.

New circuit efficiencies. Through the development and adaptation of thick-film hybrid circuitry, born of aerospace technology, almost one-half the normal electrical interconnections are eliminated. The new circuits improve electrical efficiency by 45% (135 micro-watts of power drain vs. 244 micro-watts formerly).



The new micro-circuitry in both the sensing and pacing circuits—plus the rectangular power cells—allow a 25% reduction in the volume of the generator. Thus, while generator size is reduced, power capacity is increased 50%.

Hermetic sealing of these critical hybrid circuits, plus a second overall hermetic sealing of the complete circuitry, virtually locks-out deteriorative moisture. The metal hermetic containers also provide additional protection from electromagnetic interference (EMI).

In addition, patient defibrillation can be conducted without damaging the generator.

Adapts to electrodes.

Implant procedures are not altered because the Sentry 75 is compatible with all existing GE electrodes which feature simple self-sealing, push-pull connectors. It is also adaptable to the electrodes of other manufacturers.

The pulse generator is provided as a bipolar system which, at implant, can be converted to unipolar pacing if desired. This is accomplished by simply removing the insulating label covering the metallic plate electrode on the generator's surface, and attaching it to a unipolar electrode, or to a bipolar electrode adapted for unipolar pacing.

Standardized output.

Choice of rates. Two models of the Sentry 75 pulse generator are presently available with two additional models scheduled for subsequent availability. Models differ only in pacing and hysteresis rates.

Model	Pace Rate	Hysteresis (Escape Rate)
A2075A/AD	73	63
A2075B/BD	80	70
A2075C/CD*	85	80
A2075D/DD*	73	71

*Available second quarter of 1974.

GENERAL ELECTRIC

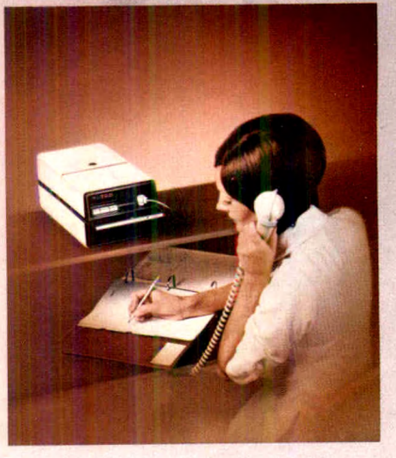
Patient management.

The Sentry 75 pulse generator has a built-in service-life indicator that is simple and easy to use. The pulse generator's pacing rate is highly dependent upon battery voltage; thus as battery voltage begins to fall near end-of-life, pacing rate will decrease. This change in rate can be easily and accurately monitored when a GE patient sensor and rate-interval computer are used. The latter is a desk-top unit which, used in conjunction with the patient sensor, enables the physician to check the patient's pacemaker over the phone between regular office visits. The patient can also be instructed to check his own rate with the sensor.

Clinical evaluation.

Laboratory tests of the Sentry 75 components were conducted for 2 years before any implants in humans were undertaken. Clinical evaluations began on a worldwide basis in November, 1972. Physicians representing more than 15 major hospitals and medical centers are participating in the program.

General Electric
Medical Systems, Milwaukee,
Toronto, Liege, Madrid



GENERAL ELECTRIC

DONTI T.M. The Pulmonary Performance Analyzer that makes every second count

In the few seconds required for a patient to perform a forced exhalation, the DONTI T.M. Pulmonary Performance Analyzer records and instantaneously displays a complete battery of sensitive spirometric parameters:

- Forced vital capacity
- FEV_1
- FEV_3
- Peak flow
- $FEV_{1\%}$
- $FEV_{3\%}$

With 10 more seconds of patient participation, the DONTI T.M. Pulmonary Performance Analyzer measures and expresses maximum voluntary ventilation (MVV) in liters per minute.

The DONTI T.M. Pulmonary Function Recorder:

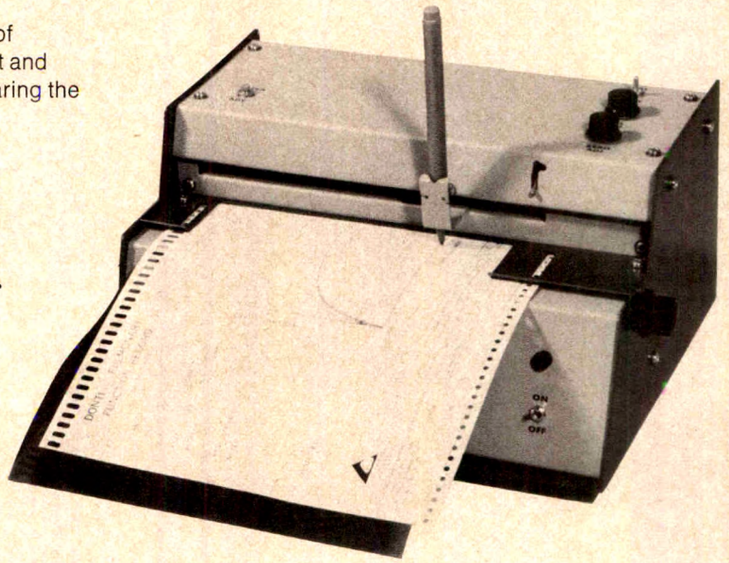
- Produces simultaneously a meaningful record for patient histories.
- Provides a basis for easily determining $FEF_{200\text{-}1200}$ and $FEF_{25\%\text{-}75\%}$.

The functional integration of the circulatory and respiratory systems makes it inevitable that disturbances in one will profoundly affect the other.

It has been noted that good spirometry can supply the clinician with most of the information he wishes to know about airway obstruction, much about restriction of the expansion of the lungs and how to distinguish these two types of physiologic defects from each other.

Spirometry has been employed as a routine presurgical procedure for assessing potential complications.

The Donti system simplifies the mechanical aspects of testing and allows the clinician to focus on the patient and proper testing technique — with no diversion to preparing the instrument or to time-consuming calculations.



For bibliography and further information on chronic obstructive pulmonary disease, please write:

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Twenty-Third Annual Scientific Session American College of Cardiology New York, New York, February 11 to 14, 1973

Method and Criteria of Selection of Abstracts

A record number of 860 abstracts were submitted to the College for consideration for presentation at the 23rd Annual Scientific Session. Each abstract was reviewed by a dual process which included review by teams of experts in 24 different areas of cardiology as well as by general cardiologists, thereby insuring that the presentations will deal with topics of current interest to a broad audience. The abstracts were graded objectively and independently from 1 to 10 with 10 being the highest score. Independent results were returned by each grader to the Bethesda office of the College. When an abstract came from a reviewer's institution, an abstention was recorded.

The scores of each abstract were then averaged by the College staff, and all abstracts receiving a grade of 7.3 and above by both expert and generalist teams were accepted for presentation. Those rated above 7.3 by one team but receiving a lower level of priority by either the generalists or the experts were individually reviewed by members of the Committee.

This year, because of the excellence of the abstracts and the augmented facilities of the program, it was possible to select a total of 235 for the final program, an increase of 15 percent over any previous year.

Eliot Corday, MD, FACC
Scientific Program Chairman

NATURAL HISTORY AND TREATMENT IN MUSCULAR SUBAORTIC STENOSIS*

Allan G. Adelman, MD; E. Douglas Wigle, MD; Clarence H. Felderhof, MD; Allan S. Trimble, MD; Wilfred G. Bigelow, MD, Divisions of Cardiology and Cardiovascular Surgery, Toronto General Hospital, Toronto, Ontario.

Some authors have suggested that surgery is rarely indicated in muscular subaortic stenosis (MSS). Others, who favour surgery, advocate mitral valve replacement rather than ventriculomyotomy or muscle resection.

Study of the natural history of 26 patients (pts.) with MSS untreated over 4 years revealed that 11 of 17 (65%) in NYHC I or II, and all 9 in NYHC III or IV deteriorated or died.

Propranolol was given to 32 pts. who were followed 3 years. All 10 pts. with latent outflow tract obstruction improved. Of 22 pts. with outflow tract obstruction at rest, only 8 (36%) improved. Of the remaining 14 pts., 1 (5%) was unimproved, 9 (41%) deteriorated and 4 (18%) died. Seven of the 9 pts. who deteriorated have undergone ventriculomyotomy.

Ventriculomyotomy was performed in 39 pts. with 3 deaths (mortality 8%). No deaths have occurred in the last 25 operations. Of 36 pts. surviving surgery, 29 (80%) improved symptomatically. Post-operative studies in 19 pts. revealed that a successful ventriculomyotomy abolished the abnormal systolic movement of the anterior mitral leaflet, the outflow obstruction and related mitral regurgitation. Left ventricular end-diastolic pressure decreased in 15 of 19 pts.

Ventriculomyotomy is a very effective operation in MSS and is indicated in symptomatic pts. not responding to Propranolol.

* Abstracts are listed alphabetically by first author.

PERSISTENT DEPRESSION OF MYOCARDIAL FUNCTION AFTER EXPERIMENTAL COXSACKIEVIRUS B3 VIRAL MYOCARDITIS

Christa O. Adesanya, MD; William P. Phear; Alan H. Goldberg, MD; Nathaniel A. Young, MD; Walter H. Abelmann, MD, FACC, Thorndike, Anesthesia and Channing Laboratories and Harvard Medical Unit, Boston City Hospital, Boston, Massachusetts

To test the hypothesis that chronic idiopathic cardiomyopathy might be a sequela of previous viral myocarditis, 35 suckling golden hamsters were inoculated i.p. with 10^6 plaque forming units of coxsackievirus B3. Twelve sham inoculated hamsters served as controls (C). Most animals sacrificed within 7 days of inoculation showed histological evidence of myocarditis, infectivity of myocardium exceeded that of serum on day 3, and 80% of inoculated animals developed neutralizing antibody titers<1:40. Ninety days later, surviving inoculated (I) animals appeared clinically healthy, showed few histologic lesions and no cardiac hypertrophy.

Left ventricular trabeculae carneae muscles were isolated and suspended in a muscle bath. Experiments were performed with the preparation contracting isometrically at a rate of 0.25/sec at 32°C. Results are summarized below:

	N	L_i (mm)	L_{max} (mm)	peak dev. tension (gm/cm^2) $[Ca^{++}]$2.2mM	$[Ca^{++}]$3.3mM
C	6	5.44±0.21	7.28±0.10	112.3±5.4	154.0±17.6
		NS	(P<0.001)	(P<0.001)	(P<0.001)
I	10	5.27±0.25	6.72±0.10	64.2±9.9	74.2±11.7

L_i = muscle length at minimal resting tension, L_{max} = muscle length at peak developed tension. Cross-sectional areas were similar. In I diminished L_{max} and developed tension at both $[Ca^{++}]$ suggests decreased compliance and depressed myocardial function. This dysfunction appears to persist for at least 90 days after subclinical viral myocarditis.

PAROXYSMAL A-V NODAL REENTRANT TACHYCARDIA FOLLOWING ATROPINE

Masood Akhtar, MD, Anthony N. Damato, MD, William Batsford, MD, Anthony N. Caracta, MD, Jeremy N. Ruskin, MD, Sun H. Lau, MD, U.S. Public Health Service Hospital, Staten Island, New York

It is well known that a critical A-V nodal conduction delay is required for the initiation of paroxysmal A-V nodal reentrant tachycardia (PAT). This critical A-V nodal delay can be achieved by appropriately timed premature atrial beats occurring within the relative refractory period of the A-V node or during A-V nodal Wenckebach cycles produced by rapid atrial pacing. Using His bundle recordings and premature atrial stimulation techniques four patients (pts) were studied before and after small doses (0.5 mg I.V.) of atropine, at comparable preceding atrial cycle lengths (A_1-A_1) and atrial premature coupling intervals (A_1-A_2), up to the point of atrial refractoriness. Before atropine, 3 pts demonstrated single atrial echo beats and 1 pt had no atrial echo beats. After atropine, sustained PAT occurred in all 4 pts. In 3 pts, PAT occurred at the same A-V nodal delay which before atropine produced only single echo beats and in the 4th pt, atropine permitted the attainment of a greater and requisite A-V nodal for PAT. PAT due to A-V nodal reentry could be distinguished from sinus tachycardia and sinus node reentrant tachycardia. It is postulated that atropine which shortens the effective and functional refractory periods of the A-V node and shortens antegrade and retrograde A-V nodal conduction time caused a critical and necessary balance between conduction within the antegrade and retrograde limbs of the reentrant circuit so that PAT could be sustained.

DOSE-RESPONSE EFFECTIVENESS OF PROPRANOLOL FOR THE TREATMENT OF ANGINA PECTORIS

Edwin L. Alderman, M.D., F.A.C.C., Mario Lopes, M.D., Donald C. Harrison, M.D., F.A.C.C., Cardiology Division, Stanford University School of Medicine, Stanford CA

A clinical trial of 10 months duration in 17 patients(pts) evaluated the response of angina to propranolol in 4 divided daily doses of placebo, 20, 40 and 80 mg, in relation to drug blood levels. Pts entered the double-blind portion of the study only after the frequency of anginal episodes was greater than 5/week during a 3 month period of single-blind placebo medication. Pts then entered 4 6-week double-blind periods, receiving each of the 4 dose levels in a random sequence. Angina frequency and nitroglycerin consumption were recorded by pts on personal diaries collected biweekly. Average exertional angina episodes per week were reduced from 8.2±2.4 during placebo medication to 5.2±1.0 (N.S.) while taking 80 mg/day, 4.8 ±1.3 ($p<0.5$) while taking 160 mg/day, and 3.3±1.2($p<.01$) while taking 360 mg/day. Physician evaluations at biweekly intervals and exercise testing during each dose period confirmed the statistical significance of the clinical response. Mild adverse effects were noted in 8 of the 17 pts and in some pts rebound withdrawal symptoms from propranolol occurred. Propranolol blood levels obtained between 100 and 180 minutes after the last tablet correlated highly with the dose and the clinical response. Propranolol doses of 80 mg/day were clinically ineffective and generally achieved blood levels below 30 ng/ml,whereas daily doses of 160 and 320 mg achieved blood levels above 40 ng/ml and were effective in reducing angina frequency and nitroglycerin consumption, and in increasing pain-free days and treadmill exercise tolerance.

EVALUATION OF THE EFFECTS OF ANTITHROMBOTIC THERAPY ON SURVIVAL FOLLOWING AORTOCORONARY BYPASS SURGERY

Mahdi S. Al-Bassam, MD; Robert J. Hall, MD, FACC; Efrain Garcia, MD, FACC; Robert D. Leachman, MD, FACC; Louis L. Leatherman, MD; Grady L. Hallman, MD, FACC; Denton A. Cooley, MD, FACC; Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Texas

Various antithrombotic regimes used emperically by various consulting Cardiology Sections of this Institute were evaluated 6 to 40 months postoperatively to determine effects on late survival (after 1 month). Coumadin (C) was favored in the early period while Persantine (P) and aspirin (A) were used alone or in combination, more frequently in the last 2 years. Therapeutic regimes were continued for a sufficient period assuring comparable patient enlistment into each therapeutic group. Charts, letters to patients and information from private doctors were reviewed to collect data on C, P, & A regimes. Of the 1404 patients operated at this Institute from August 1969 to September 1972, adequate follow-up drug data were available on 1078 patients, 60 of whom died in the follow-up period. The "life survival curve" (Cutler) of the 1078 subgroup was closely similar to the curve for the total series of 1404 patients. Therapy prescribed, singly or in combination, was as follows: C, 557 patients; P, 430; A, 358; and no C, P, A, 243.

Follow-up	C	P	A	No CPA	All Pts
6 mo.	99.1%	99.1%	99.7%	94.6%	97.9%
18 mo.	95.6%	96.6%	97.4%	91.7%	94.9%
30 mo.	93.1%	94.2%	96.2%	89.0%	92.2%

All percentages are related to cumulative survivals. Higher survival was associated with A alone or in any combination while C and P were close to the average rate of attrition. No antithrombotic therapy was associated with a decreased survival in the observed group.

ENDOMYOCARDIAL BIOPSY: ITS CLINICAL APPLICATION.

Ali, N. Ferrans, V.J., Banks, T., and Roberts, W.C. D. C. General Hospital and National Heart & Lung Institute, Bethesda, Maryland.

Fifty patients (pts) with (c) suspected cardiomyopathy (CM) in the presence or absence of a systemic disease were selected for endomyocardial biopsy in an attempt to clarify the etiology of the CM. The primary diagnoses included myocarditis (viral), bacterial endocarditis, sarcoidosis, sickle cell disease, eosinophilic leukemia, systemic sclerosis, myxedema, throtoxicosis and chronic alcoholism. Three techniques were used i.e. Konno's Bioptome in 25 pts, GFB biopsy catheter either alone in 20 or introduced through an end hole catheter in 5. Two to 5 specimens were obtained. Overall success rate was 92%. Complications included ventricular tachycardia (TV) in a pt c sarcoidosis and recurrent VT, ST-T changes in 1 pt and right bundle branch block in 4. All the changes were transient. No other immediate or late complications secondary to the procedure were noted. The structural changes observed were: interstitial fibrosis, cellular hypertrophy and degenerative changes of edema, lipid deposition, myofibrillar loss, sarcoplasmic reticular dilatation & mitochondrial damage. The degree and extent of these changes correlated c the duration and severity of heart disease. No viral particles but nuclear & nucleolar alterations were found in 2 pts from whom Coxsackie B viruses were isolated. Tuboreticular structures were found in a thyrotoxic pt. Alcoholic & non-alcoholic pts c CM could not be distinguished morphologically.

THE EFFECTS OF ATRIAL PACING SITE ON A-V NODAL FUNCTION
Fernando Amat, MD; Pablo Denes, MD; Delon Wu, MD; Raymond J. Pietras, MD, FACC; Kenneth M. Rosen, MD, FACC, University of Illinois, Chicago, Ill.

The effects of atrial pacing site on A-V nodal function was evaluated in 14 patients. Three sites were tested: 1) High lateral right atrium (HRA); 2) Low lateral right atrium (LRA), and 3) Mid-coronary sinus (CS). His bundle (H) electrograms were measured using electrode catheters. The atrial electrogram (A) on the H recording was considered to reflect activation of low septal right atrium (LSRA). A-H was compared at a paced rate of 90/min. A-H (mean ± SEM) with HRA, LRA, and CS pacing was respectively 154 ± 21 msec, 148 ± 17 msec, and 114 ± 14 msec. A-H was significantly shorter during CS pacing when compared to both HRA and LRA pacing ($p < 0.01$). The mean paced rate inducing type 1 block proximal to H was 143 ± 8 beats/min with HRA pacing, 145 ± 9 beats/min with LRA pacing, and 146 ± 10 beats/min with CS pacing (NS). Mean A-V nodal effective and functional refractory periods, measured at identical cycle lengths, were respectively 436 ± 75 and 504 ± 47 msec from the HRA, 450 ± 79 and 502 ± 53 msec from the LRA, and 457 ± 73 and 490 ± 42 msec from the CS. These were not significantly different. In conclusion, A-H interval was shorter with CS pacing when compared to HRA and LRA pacing at equivalent rate. This shortening did not appear to reflect a decrease in A-V nodal conduction time, since other indices of A-V nodal function were identical when comparing the three pacing sites. The short A-H during CS pacing may reflect simultaneous activation of LSRA and A-V node from depolarization proceeding from the CS. The site of impulse formation must be considered when evaluating A-V nodal function using A-H interval.

K^+ MEDIATED RELEASE OF OUABAIN FROM PURKINJE CELLS
Gary J. Anderson, MD, Indiana University School of Medicine, Indianapolis, Indiana.

The purpose of this study was to determine 1) the effect of elevating potassium concentration ($[K^+]_o$) on the binding of ouabain (OUA) to canine Purkinje fibers and 2) the electrophysiological consequences of changes in OUA binding subsequent to elevation of $[K^+]_o$. Conventional microelectrode and scintillation counting techniques were utilized. In 10 experiments, Purkinje cells were initially exposed to tritiated OUA (H^3-OUA) (0.3×10^{-6} M) until phase 4 depolarization and a reduction in maximal diastolic potential occurred. The preparation was then exchanged with an identical solution containing non-labelled OUA and exposure was continued until the cells depolarized to 47.1 ± 4.3 mV. After elevation of $[K^+]_o$ from 2.7 mEq/l to 5.4 mEq/l membrane potential increased to 61.2 ± 1.3 mV. Concomitant with this increase in membrane potential, mean H^3-OUA concentrations from the tissue bath effluent rose 49.14% (range 21.7%-198.7%) within 2 minutes indicating release of previously bound H^3-OUA. Despite continued superfusion with non-labelled OUA bath concentrations of H^3-OUA remained above expected values calculated from standard dilution curves, indicated continued release of H^3-OUA. This potentiated release of H^3-OUA paralleled the time course of increase membrane potential. Similar studies conducted on metabolically inactive cells failed to demonstrate the potentiated release of H^3-OUA from Purkinje cells in response to elevation of H^3-OUA. It is concluded that reversal of digitalis toxic manifestations of OUA are reversed by elevation of $[K^+]_o$ and may be causally related to cellular release of ouabain.

EARLY SURGICAL INTERVENTION FOR COMPLICATED ACUTE MYOCARDIAL INFARCTION: INITIAL AND LONG-TERM RESULTS.
Ezra A. Amsterdam, MD, FACC; James L. Hughes, MD; Richard R. Miller, MD; Albert Iben, MD; Edward Hurley, MD; Robert Zelis MD, FACC; Dean T. Mason, MD, FACC, Univ. Calif., Davis, Calif.

The high mortality associated with the early, severe complications of acute myocardial infarction (AMI) has stimulated increasingly aggressive treatment of these syndromes. Direct cardiac surgery now provides a rational approach to complicated AMI intractable to medical therapy. We have performed corrective cardiac surgery on 9 patients (pts) within 14 hrs-8 days (mean 4 days) of occurrence of complication. Complications of AMI in these pts were: cardiogenic shock (n=5), recurrent ventricular tachycardia (VT)(n=2) and threatened extension of established AMI (n=2), all of which were unresponsive to conventional medical therapy. Diagnostic evaluation, consisting of left heart catheterization, left ventriculography and selective coronary arteriography, was performed in all pts without the aid of mechanical circulatory assist to identify any surgically remediable lesions. Catheterization incurred no morbidity or mortality. As a result of angiographic evaluation, the following surgical procedures were performed: for shock- closure of ventricular septal defect (VSD) 2 pts, combined closure of VSD and infarctectomy 1 pt, infarctectomy 2 pts; for recurrent, intractable VT- aorto-coronary saphenous vein bypass grafts (CBG) 2 pts; for threatened extension of AMI- CBG 2 pts. Results: Complete reversal of AMI complications in 7 pts (78%)(4/5 shock, 2 VT, 1 threatened extension of AMI), 1 operative death, 2 intraoperative infarctions. There are 8 long-term survivors (89%)(mean follow-up 13 mos, range 1-38 mos) 7 of whom have returned to full activity. Early evaluation and direct surgical intervention are feasible for complications of AMI.

REGIONAL ISCHEMIC FREE FATTY ACID METABOLISM WITH ANGINA.
Carl S. Apstein, MD, Susan Kline, MD, Nadya Keller, PhD, Norman Brachfeld, MD, FACC, Cornell Medical Center, N.Y., N.Y.

Sixteen patients with angiographically proven coronary disease were paced to provoke angina pectoris with concurrent simultaneous coronary sinus (cs), and arterial (art.) metabolic sampling. Thirty-eight samplings demonstrated cardiac lactate production and were considered to be the efflux from ischemic regions; 96 samplings showed lactate extraction and were classified as non-ischemic efflux. Fractional free fatty acid (FFA) extraction $((FFA_{art.})-(FFA_{cs}))\div(FFA_{art.})$ at rest was 0.19±.02. With pacing, ischemic fractional FFA extraction decreased by 37% to 0.12±.01 ($p < .05$), but non-ischemic FFA extraction did not change. FFA oxidation was measured by infusing a tracer amount of ^{14}C-FFA (^{14}C-palmitate bound to human albumin) to achieve an arterial steady-state level, and quantitatively collecting $^{14}CO_2$ in the coronary sinus samples. Fractional ^{14}C-FFA oxidation, $((^{14}CO_{2cs})-(^{14}CO_{2art.}))\div((^{14}C\text{-}FFA_{art.})-(^{14}C\text{-}FFA_{cs}))$, in the resting state was 0.54±.03. With pacing, regional ischemic efflux demonstrated a 31% increase in fractional ^{14}C-FFA oxidation to 0.71±.05 ($p < .01$) but non-ischemic FFA oxidation was unchanged. Thus, the regional ischemia associated with pacing-induced angina results in a significant decrease in fractional FFA extraction with an increase in fractional FFA oxidation, making myocardial lipid deposition unlikely. These clinical results stand in sharp contrast to isolated hypoxic animal heart experiments, where marked FFA and triglyceride tissue accumulation occurs.

PACEMAKER CURRENT IN CARDIAC PURKINJE FIBERS: EVIDENCE FOR DEPENDENCE ON THE NA-K PUMP

Ronald S. Aronson, MD; Jeremiah M. Gelles, MD; Brian F. Hoffman, MD, College of Physicians & Surgeons of Columbia University, New York, New York.

We have previously shown that ouabain greatly diminishes or abolishes the current (IK2 or pacemaker current) presently considered to be responsible for spontaneous diastolic depolarization in Purkinje fibers of the sheep. Since ouabain is a relatively specific inhibitor of the Na-K pump we were led to test the effect of other pump inhibitors on IK2. The effects of substitution of Li for Na and of 2,4-dinitrophenol (DNP) on IK2 were studied using a two-microelectrode voltage clamp technique in shortened cardiac Purkinje fibers of the sheep. Isolated fibers were perfused with Tyrode solution (K, 4.0mM, T, 36°C) the Na of which was isosmotically replaced with Li (except for 12mM $NaHCO_3$) or to which DNP, 0.2mM, was added under test conditions. Exposure to Li Tyrode solution greatly reduced or abolished IK2. This current reappeared on readmission of Na Tyrode solution. DNP also greatly attenuated IK2. Action potentials which under control conditions showed spontaneous diastolic depolarization did not show such activity after exposure to Li Tyrode solution or to DNP. The dramatic reduction or abolition of the pacemaker current under various conditions that inhibit the Na-K pump suggests that the integrity of this pump is in some way necessary for the generation of this current.

CRITERIA FOR THE VALIDITY OF THE RISE IN LEFT VENTRICULAR END DIASTOLIC PRESSURE FOLLOWING PACING INDUCED ANGINA

Raphael Balcon, MD, FACC; Roger Wilkinson, MB; Warren Walsh, MB, MRACP; Anthony Rickards, MB, MRCP. London Chest Hospital, London, England.

85 patients being investigated for angina have been studied at cardiac catheterisation. With continuous measurement of LVEDP the heart rate (HR) was increased by pacing from an initial rate of 100 bpm, increasing by 10 bpm each minute. If AV block occurred during RA pacing, the catheter was advanced to the RV and the test continued until either the maximum rate of 180 bpm was reached or the patient complained of cardiac pain. At the end of each minute the pacemaker was switched off and LVEDP recorded for 10 beats in sinus rhythm. 4 patient groups were identified. A (47 patients) with CAD who developed angina during pacing, B (12 patients) with CAD without induction of angina, C (13) and D (13) had no CAD but group C complained of pain during pacing. Group D were considered normal. No differentiation between the groups was apparent from LVEDP during pacing. Following switch-off of pacing the RR interval, pre a, a wave and post a pressures were measured in each patient. The relationship between pre a and a ($r=0.96$) and pre a and post a ($r=0.95$) remains constant for any individual. With increased HR there was no significant change in LVEDP from control in groups B, C, D. Only in group A at the induction of angina (p 0.001) and 10 beats before (p 0.05) did LVEDP rise significantly. The magnitude of the rise in LVEDP is proportional to the HR attained before switch off of pacing. Thus a rise of 1mm Hg at 100-120 bpm, 3mm Hg at 130-150 bpm and 5mm Hg at 160-180 bpm was seen in 70% of group A and only 23% of group D (normal). These figures provide more accurate guidelines for the definition of an abnormal LV response to pacing.

RELATION OF EARLY POSTOPERATIVE MYOCARDIAL INFARCTION TO PATENCY OF AORTOCORONARY BYPASS GRAFTS AND TO UNGRAFTED CORONARY ARTERIES

Jose L. Assad-Morell, MD; Gerald T. Gau, MD, FACC; Robert L. Frye, MD, FACC; Daniel C. Connolly, MD, FACC; George D. Davis, MD; Gordon K. Danielson, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

To study the incidence of early transmural myocardial infarction (TMI) after saphenous-vein bypass graft and its relationship to graft patency and diseased ungrafted coronary arteries, we analyzed the preoperative and postoperative (PO) electrocardiograms (ECG) and vectocardiograms (VCG) of 572 patients (pts) operated on from 1969-1972 inclusive. Standard ECG and VCG criteria for diagnosis of TMI were used, and the angiograms of pts with early PO-TMI were reviewed. TMIs occurred in 67 (12%) of the pts. Nearly all of them were documented within 24 hours after operation, and the rest within 72 hours. The pts comprised 15 (5%) of the 295 who had had TMI prior to surgery and 52 (19%) of the 277 who had not. There were 47 TMIs within the distribution of the grafted vessels and 17 in the distributions of vessels that had been severely diseased but not grafted. (Three were in the distributions of angiographically normal vessels.) Repeat angiography, performed in 36 of the 67 cases of early PO-TMI, showed that 32 of the infarcts in this group were within the distribution of the grafted vessel. The grafts were patent in 16 of these pts and there was graft occlusion in 16. The 12% risk of early postoperative TMI is substantial. Clearly, the occurrence of early PO-TMI is not a reliable indication of graft occlusion, for 25% of all TMIs were in the distribution of diseased but ungrafted arteries, and among the group of 32 who developed TMI in the distribution of the grafted artery and were studied angiographically afterward, as many grafts were patent as occluded.

EFFECTS OF NITROGLYCERIN ON REGIONAL LEFT VENTRICULAR LENGTH-TENSION RELATIONS AFTER CORONARY OCCLUSION

Vidya S. Banka, MD; Monty Bodenheimer, MD; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Controversy has existed concerning the value of nitroglycerin (TNG) in acute coronary disease. To better define this issue, the effects of TNG (30ug/Kg intravenously) on local tension and length characteristics of the ischemic (IZ), border (BZ) and nonischemic (NZ) zones of the left ventricle were studied in 10 open chested dogs using Walton-Brodie strain gauges and mercury-in-silastic segment length gauges. In the BZ, the pre-ejection tension (PET) increased by 30.9 ± 10.9%, ejection tension (ET) by 44.0 ± 8.5% and the rate of tension rise (DT/dt) by 41.7 ± 7.0% ($p<0.01$) in all observations recorded 15 minutes (min), 30 min., one, two and three hours after anterior descending coronary ligation (CL). NZ exhibited a parallel increase in all tension parameters. Segment length (SL) in the BZ decreased by 24.5 ± 1.3% at 15 and 30 min of CL and by 12.7 ± 1.6% after 1-3 hours of CL ($p<0.01$). NZ demonstrated a consistent decline of 23.3 ± 2.4% in SL regardless of the duration of CL. Maximal response to TNG both in tension and length parameters was observed within 30 seconds to 1 min and was simultaneous with 26.7 ± 1.9% decrease ($p<0.01$) in blood pressure and an insignificant (7.1 ± 0.9%) increase in heart rate. IZ exhibited no significant response either in tension or length parameters. In summary, TNG improves the contractile characteristics of the nonischemic and border zones following coronary occlusion without affecting the central ischemic zone. However, the border zone exhibits a progressive decrease in length response, presumably due to decreasing compliance.

VALUE OF CORONARY COLLATERALS, PATHOLOGIC Q WAVES AND SEGMENTAL LOCATION AS DETERMINANTS OF REVERSIBILITY OF ASYNERGY IN CORONARY HEART DISEASE

Vidya S. Banka, MD; Monty Bodenheimer, MD; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

The selection of patients for aorto-coronary bypass surgery depends largely on the potential for improvement in asynergic zones. To determine which factors may predict whether or not asynergy is reversible, the response of asynergic zones to sublingual nitroglycerin (1/150 grs) was studied angiographically in 35 patients and was correlated with the presence or absence of collaterals and pathologic Q waves in the corresponding zone of asynergy. Of the 21 zones to which collaterals were demonstrable 19 (90.4%) improved and only 2 (9.6%) remained unchanged ($p<0.001$). Both of the unimproved segments were located in the inferior wall. Of the 31 zones to which collaterals were not demonstrable, 14 (45.1%) improved while 17 (54.9%) remained unchanged. Pathologic Q waves were present in 30 zones of which 22 (70.3%) were unresponsive while 8 (29.7%) improved ($p<0.001$). Of the 34 zones which did not have corresponding Q waves, 27 (73%) improved but 7 (27%) remained unchanged ($p<0.001$). The relative location of the asynergic zone also influenced the chances of reversibility. Of the 25 anterior wall segments 18 (72%) improved while 7 (28%) did not. In contrast only 7 (33%) of the 21 apical segments improved and 14 (66%) remained unchanged. Of the 18 inferior wall segments 10 improved and 8 showed no response. In summary, the presence of collaterals and the absence of pathologic Q waves in the corresponding segments appears predictive of the potential reversibility of the asynergic segment. Apical asynergy responds less frequently than anterior or inferior zones.

DIFFERENTIAL EFFECTS OF DIGITALIS ON CONTRACTION OF ISCHEMIC, BORDER AND NONISCHEMIC VENTRICULAR ZONES FOLLOWING CORONARY LIGATION

Vidya S. Banka, MD; Kul D. Chadda, MD; Monty Bodenheimer, MD; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

The effects of digoxin (priming dose 0.04 mg/Kg; 0.01 mg/minute infusion) on local tension and length characteristics following coronary ligation were studied in 20 dogs utilizing Walton-Brodie tension and mercury-in-silastic length gauges. In the nonischemic zone, digoxin augmented pre-ejection tension (PET) by 42.0 $\pm$ 5.6%, ejection tension (ET) by 60.4 $\pm$ 12.1%, and rate of tension rise (DT/dt) by 46.4 $\pm$ 9.6% when administered 15 minutes to two hours following ligation. Similarly, the border zone increased by 49.4 $\pm$ 10.8% in PET, 62.9 $\pm$ 11.5% in ET, and 40.5 $\pm$ 5.9% in DT/dt ($p<0.01$ in all parameters). In the ischemic zone, digoxin given 15 minutes after ligation produced 27.3% increase in PET and 20.0% in DT/dt with no change in ET. However, when started 30 minutes after ligation, no significant changes occurred in tension parameters and an actual 3-5% decline was observed when infused one and two hours after ligation (compared to a 5-8% decrease in control dogs). Segment lengths were essentially unchanged in all studies. In summary, digitalis uniformly increases contraction of nonischemic and border zones following coronary ligation. However, effects on both contraction and aneurysmal bulging in the ischemic zone are minimal.

AORTA-RIGHT PULMONARY ANASTOMOSIS - LONG TERM PROBLEMS AND RESULTS AFTER TOTAL CORRECTION

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The results in 95 cyanotic patients one to 6 years after aorta to left pulmonary anastomosis are presented. Spontaneous closure of the shunt was rare (3%), as was chronic heart failure (2%) and pulmonary vascular disease (2%). There was an unusually high mortality after total correction in Fallot and pulmonary atresia. Seven of 36 patients died with good anatomical correction and in all the postoperative main pulmonary artery pressure at surgery was high. Lung histology did not show pulmonary arteriolar disease and the problem appeared to be caused by hypoplasia of pulmonary arteries proximal to the shunt. Factors which predispose to this serious state are the leaving of a shunt which only perfuses the right lung. This was dangerous when the operation had been performed in Fallots under the age of 3 and in pulmonary atresia under 5 years. Upward kinking of the right pulmonary artery, which is common with this anastomosis, may prevent any flow into the rest of the pulmonary tree and if the right ventricular outflow is atretic, there may be no flow to stimulate growth. The operation has definite place in therapy but early postoperative investigation is recommended, irrespective of clinical result in order to see distortion of pulmonary tree. If there is only perfusion of one side, early total correction is recommended. In the child with pulmonary atresia who may not have reached an ideal size for homograft correction, a left sided shunt may be required to ensure growth of the left pulmonary artery.

LEFT MAIN CORONARY ARTERY DISEASE--IS SURGERY ALWAYS INDICATED?

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Recent reports regarding left main coronary artery disease (LMCAD) suggest that it's presence, in itself, is indication for bypass surgery. We have followed 11 operated patients (OP) and 10 unoperated patients (UP) with >50% demonstrable LMCAD from 5 to 74 mos following catheterization (C). Although average onset of CAD to C was 50 mos (1-144), all but 2 patients (pts) had C because of accelerated angina. The OP and UP were comparable in all clinical and C parameters. All pts had 2 or 3 vessel involvement. Total occlusion was present in 25 vessels. Collaterals, calcification and significant left ventricular (LV) dysfunction (ejection fraction < 40%) were present in 14, 8, and 7 pts respectively. ECG's showed infarction, LVH, or ST changes in 13, 11, and 16 pts respectively. Stress tests were markedly positive (> 3mm) in 4/4 pts stressed. The only morbidity in 25 C was one episode of ventricular fibrillation. Of the 11 OP, 5 had double and 6 triple bypass grafts. Mortality from surgery was 9% (1/11). 9 OP have been followed 11 mos (3-27). Relief of pain is complete in 6, moderate in 2 and worse in 1 pt. 4/10 died of cardiac causes 13 mos (6-24) after C. One UP died of a CVA 50 mos after C, and 5/10 are alive 35 mos (13-74) after C. Three UP are the same or worse and 2 improved. Two UP restudied at 6 and 3 year intervals showed progression of LMCAD. We conclude that even though the overall mortality is increased in UP with LMCAD, the long term followup and surgical results are not sufficient to justify prophylactic operation for this disease. The average interval in UP from onset of CAD to death or followup was 74 mos (18-166); thus, the association of incapacitating angina should be the indication for surgery.

EFFECTS OF CARDIAC ARRHYTHMIAS ON AORTOCORONARY BYPASS GRAFT BLOOD FLOW VELOCITY IN MAN

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The influence of cardiac arrhythmias on aortocoronary saphenous vein bypass graft blood flow velocity (AGFV) has not been described. Utilizing the Doppler ultrasonic flowmeter catheter AGFV was measured in a total of 19 grafts in 16 conscious patients (pts.) during a variety of cardiac arrhythmias. Atrial (atr.) and ventricular (ventr.) premature depolarizations reduced peak AGFV by 20 to 90%, dependent on their extrasystolic coupling intervals. Post-extrasystolic sinus beats resulted in an AGFV "overshoot", with greater rebound related to longer preceding R-R intervals. Sustained atr. tachycardia (tachy.) produced an initial decline of AGFV which was followed by a gradual rise to levels greater than those recorded during the control period. Nineteen transient episodes of ventr. tachy. reduced peak AGFV by an average of 50%, (control AGFV ($\bar{X}\pm$1SD) = 28±11 cm./sec., ventr. tachy. = 14±8 cm./sec. $P < 0.001$). In the setting of sinus rhythm, atrioventricular dissociation and ventr. tachy., fusion beats and properly timed atrial systoles augmented AGFV. In 2 pts., AGFV alternation was recorded during ventr. tachy. at ventricular rates greater than 150/min. Cardiac arrhythmias influenced native coronary and AGFV in a similar manner when such measurement was obtained at these 2 respective anatomic sites in the same subject. These findings indicate the adverse influence of cardiac arrhythmias on AGFV and suggest an aggressive approach to their treatment.

A LOOP ELECTRODE SYSTEM FOR TEMPORARY RIGHT ATRIAL PACING

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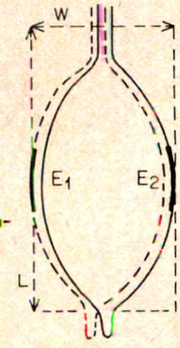
Temporary right atrial pacing (RAP) is infrequently utilized because of the problem of maintaining a stable position of the electrodes (E). To circumvent this problem, we devised a loop-mounted E system which conforms to the walls of the RA maintaining stable contact. Its resiliency allows it to be inserted into a protective catheter in the collapsed state and thus be passed from a peripheral vein into the RA. Once extruded from the catheter, it expands as far as the RA will permit. It is constructed of a pair of insulated wires with E_1 and E_2 on either side of the loop. Width W=50 mm, length L=120 mm. An hexagonal shape has also been used, as well as different sizes. To date, it has been successfully used in 3 CCU patients (pts) for relatively long-term RAP: 2 pts for rate correction of low cardiac output, 6 and 15 days; one pt. for atrial overdrive suppression of PVCs, 9 days. It has also been used in brief RAP studies in 6 pts. RAP was essentially constant in all cases. Two additional pts could not be paced due to (a) 2 other wires and 1 catheter in the RA, and (b) anatomic variation in selected venous approach. No complications in any case.



CALCIFIC AORTIC INSUFFICIENCY

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Calcification of the aortic valve (AV) is usually associated with at least some stenosis of the valve. We have observed an unusual group of patients with pure aortic insufficiency (AI) and calcified AV. Twenty-six patients had pure calcific AI (no associated stenosis), representing 8.3% of 314 patients with AV disease of any type, and 10.7% of 243 patients with any degree of AI. Nineteen (73%) males and seven (27%) females ranged in age from 25 to 75 years (mean 51). 23% were younger than 40. Sixteen (62%) had rheumatic heart disease, one had luetic AV disease, one had congenital bicuspid valve and eight (31%) had AI of undetermined etiology. Twenty-two patients (88%) had an aortic systolic ejection murmur. AV calcification was detected by plain chest films in only four patients (17%) and by routine image intensification fluoroscopy (before catheterization) in fifteen patients (71%). The remaining 29% had the calcification of the AV detected during catheterization.

AV calcification was severe in nine patients (35%), moderate in eleven (42%) and minimal in six (22%). AI was severe in twenty patients (77%), moderate in five (19%), and minimal in one (4%). Nineteen patients (77%) had reduced left ventricular contractility. Sixteen (67%) had low cardiac index. Eighteen had normal coronary arteries and three had obstructive coronary artery disease. Aortic stenosis was misdiagnosed as the predominant lesion in fourteen patients (54%), prior to catheterization. This series demonstrates that all patients with calcified AV and ejection murmurs do not necessarily have aortic stenosis. Pure calcific AI is a distinct entity, more common that previously suspected.

PROLAPSE OF THE POSTERIOR LEAFLET OF THE MITRAL VALVE ASSOCIATED WITH SECUNDUM ATRIAL SEPTAL DEFECT

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The association of prolapse of the posterior leaflet of the mitral valve (PPLMV) with secundum atrial septal defect (ASD) has recently been reported, but the incidence and features of this association have not been defined. Analysis of right anterior oblique left ventricular (LV) cineangiograms in 54 patients (pts.) with secundum ASD revealed evidence of PPLMV in 20 (37%).

In 9 of these 20 pts. there was no clinical evidence of a mitral lesion, thus the incidence of unsuspected PPLMV with secundum ASD was 20% (9 of 43 pts.). Of the 11 pts. with clinical evidence of a mitral lesion, 9 had a pansystolic murmur and only 2 had a midsystolic click, one of whom also had a late systolic murmur.

The ECG revealed a prolonged Q-T interval in 9 pts. T wave inversion was present in leads II, III and AVF in 5 pts., and in V_5 and V_6 in 4 pts. Atrial fibrillation was present in 3 pts.

Analysis of the angiographic anatomy revealed that the prolapse was triscalloped in 4 pts., biscalloped in 11 and uniscalloped in 5. Mitral regurgitation (MR) was present in 12, including the 11 pts. with clinical signs of a mitral valve lesion. Three pts. with moderate or severe MR had triscallop prolapse. LV wall motion studies in 7 pts. with MR revealed decreased shortening of the LV basal diameter with increased shortening in the long axis.

We conclude that the association of PPLMV with secundum ASD is very common and may be present in the absence of any clinical evidence of a mitral valve lesion.

PERMANENT CARDIAC PACEMAKER FOLLOW UP

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Patients with permanently implanted pacemakers require constant realistic follow up in order to recognize failures of the system. Random recovery of pacemakers from the community was used as a means of identifying pacemaker patient physicians; their patterns of patient follow up were then assessed. From 475 recovered pulse generators 172 persons were identified as patients' "pacemaker physicians". 104 of these physicians were interviewed and responses to a specific series of questions were tabulated and analyzed. Interviewees included internist-cardiologist 28.9% (30), internist 25% (26), thoracic surgeon 17.3% (18), general surgeon 7.7% (8), general practicioner 19.2% (20), other 1.9% (2). Evaluation of experience showed that 57.7% (60) followed 1-8 patients, 19.2% (20) 9-24 patients, and 23.1% (24) 25-200 patients with pacemakers. Of the total group 37.5% (39/104) had a realistic follow up plan; 60% (18/30) of internist-cardiologists, 33.3% (6/18) of thoracic surgeons, and 23% (6/26) of internists had realistic plans. 62.5% (15/24) of physicians with the greatest experience used a magnet regularly while checking pacemaker function; although most pacemakers implanted today are demand type, only 5% (3/60) of physicians with the least experience used the magnet.

It is concluded that: 1) permanent pacemaker patients require more formal and stringent follow up than they receive at the present time, and 2) design characteristics of pacemaker systems should take the expertise of the physician-user into account.

THE FREQUENCY AND PROGNOSIS OF VENTRICULAR ECTOPIC BEATS IN MIDDLE-AGED MEN

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The frequency, associations and prognostic importance of ventricular ectopic beats (VEB) were studied in 2,451 U.S. railway men and 8,319 rural European men ages 40-59 and free of coronary disease (CHD) at entry. VEB frequency in routine resting and post-exercise electrocardiograms (ECG) increased with age, and was twice as great in "high risk" men of the upper 20% of a coronary risk score (computed from the primary risk factors) ($P<.01$). VEB were also concentrated in men having other ECG abnormalities. The crude risk ratio for 5-year deaths among men having any rest or post-exercise VEB was 1.9 compared to those with no VEB. The simple univariate regression of deaths according to frequency of VEB gave a significant slope ($t = 3.1$), and it remained significantly positive after adjustment for the presence of other ECG abnormalities and primary risk factors. However, poor prognosis for CHD and death, according to the frequency of VEB, was concentrated among men having highest risk score based on blood pressure, serum cholesterol and smoking habit. We conclude that VEB are possibly significant independent harbingers of future manifest CHD and sudden death but probably only in the presence of other ECG or clinical evidence of myocardial disease, or multiple and elevated CHD risk factors. Higher grade of VEB (pairs, runs, and early beats) were too rare in short term monitoring of the general population to analyze fruitfully.

REGIONAL MYOCARDIAL BLOOD FLOW FOLLOWING CORONARY OCCLUSION IN UNANESTHETIZED NORMAL AND HYPOXEMIC DOGS.

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Regional distribution of coronary blood flow in the immediate post-infarction period was studied in chronically hypoxemic (Hpx) and normal unanesthetized dogs. Surgical transposition of the caudal vena cava to the left atrium was produced 18-30 months prior to coronary occlusion. Left ventricle weight to body weight was not significantly changed but right ventricular weight to body weight was decreased 25% ($p<.05$). Arterial O_2 saturation was 70.0 ±4.9(SD)%. A left atrial tube and an inflatable cuff were placed around the left circumflex coronary artery in 5 Hpx and 3 normal dogs, and the left anterior descending coronary artery in 5 normal dogs. After recovery (7-14d) 15 μ tracer microspheres (TM) labeled with ^{85}Sr, ^{141}Ce, or ^{51}Cr were injected into the left atrium just prior to occlusion of the coronary cuff, 5 min and 24 h after occlusion. Gross infarct size in normal dogs was 17±7% of ventricular mass and 6±8% in Hpx dogs. The TM ratio of infarcted to non-infarcted tissue in the endocardial half of the myocardium during control, 5 min and 24 h post-infarction was 0.97±0.23 (SD), 0.16±0.04, and 0.33±0.11 respectively in normal dogs, and 0.96±0.11, 0.56±0.32, and 0.81±0.41 in Hpx dogs. In the epicardial half of the myocardium the ratios were 0.89±0.04, 0.31±0.10, and 0.61±0.17 in normal dogs and 1.07±0.33, 0.80±0.53, and 0.97±0.34 in Hpx dogs. In both normal and Hpx dogs there was significant increase in blood flow to the infarcted area at 24 h compared to 5 min post-occlusion. With chronic Hpx there was greater blood flow to the infarcted tissue resulting in smaller infarct size than in normal dogs. These findings suggest that chronic hypoxia induces myocardial changes that are protective when infarction occurs.

LEFT VENTRICULOGRAPHY IN PATIENTS WITH THE ANGINAL SYNDROME AND NORMAL CORONARY ARTERIOGRAMS

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Left ventriculography, heretofore, has not been subjected to detailed investigation in patients with the anginal syndrome (AS) and normal coronary arteriograms. The left ventriculograms, obtained in the right anterior oblique (RAO) projection, of 45 patients (24 females, 21 males), mean age 47.1 years, were analyzed utilizing the one-plane cineangiographic measurement of left ventricular volume. Tracings of end-systole and end-diastole were made from the cineangiograms in the RAO projection. The ejection fraction (EF) was computed from the ratio of left ventricular systolic to diastolic volume. In addition, the percent change for both longitudinal axis (LA) and transverse axis (TA) that occurred during ventricular systole was analyzed. The EF for the 24 females in the study group ranged from 0.647 to 0.915 (mean 0.818), and for the 21 males ranged from 0.658 to 0.895 (mean 0.788). The mean percent change in the LA and TA which was observed during ventricular systole was 31.2% and 51.6% in the female sub-group, and 26.3% and 49.7% in the male sub-group, respectively. The high values for EF (mean 0.803, SD 0.0627, SE 0.0133, SEE 0.0002, ($P < .001$), compared to reported normals, suggest that hyperdynamic ventricular contraction (HVC) may be a contributing factor to the pain typical of AS in patients without angiographically demonstrable atherosclerotic lesions of the coronary arteries. In conclusion, HVC, as suggested by markedly increased EF and high degree of LA and TA shortening, could produce a state of increased myocardial oxygen consumption resulting in ischemic heart pain, and might explain the salutary effect of beta-adrenergic blockade and nitrites in some of these patients.

Q WAVES AND ASYNERGY: PREDICTIVE VALUE AND HEMODYNAMIC SIGNIFICANCE OF ANATOMIC LOCALIZATION

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To better delineate the significance of pathologic Q waves (≥.04 sec) in predicting location and functional effect of asynergy, 124 consecutive patients with asynergy were reviewed. 105 had coronary artery disease and 19 were classed as cardiomyopathy (CM) (diffuse hypokinesis and normal coronary arteriograms). 57 patients (54%) had pathologic Q waves; 27 anterior, 29 inferior and one both. Anterior Q's denoted asynergy in 27 of 27 (100%), anterior asynergy in 26 of 27 (96%) and frank aneurysm (akinesis or dyskinesis) in 22 of 27 (78%). Inferior Q's indicated asynergy in 26 of 29 (90%), inferior asynergy in 21 of 29 (78%) and aneurysm in 9 of 21 (31%). Conversely, of 47 frank aneurysms, 83% had Q's. Anterior aneurysms had Q's in 29 of 36 (80%) while inferiors had 13 of 15 (86%). Hemodynamically, the left ventricular end-diastolic pressure (LVEDP) was elevated in 15 of 27 (56%) with anterior Q's versus only 7 of 22 (31%) with inferior Q's ($p<.025$). Anterior asynergy alone was associated with an elevated LVEDP in 13 of 28 (46%) contrasted with 6 of 21 (22%) with inferior asynergy. Patients with combined or diffuse asynergy had elevated LVEDP in 43% and 45% respectively. Of the 19 patients with CM none had Q's. In summary, pathologic Q waves correlated highly with the presence of asynergy, accurately localized the site of the aneurysm and aided in predicting the degree of left ventricular dysfunction. Q's were not seen in cardiomyopathy.

BENEFICIAL EFFECTS OF LIDOCAINE ON INCIDENCE OF VENTRICULAR FIBRILLATION DURING CORONARY OCCLUSION IN DOGS.

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Several studies have questioned the efficacy of lidocaine in reducing the incidence of ventricular fibrillation (VF) shortly after acute myocardial infarction (AMI), when arrhythmogenic mechanisms are believed to be different from those operative several hours later. To determine whether lidocaine inhibits occurrence of early VF, open-chest anesthetized dogs were randomized into 3 groups: a control group (saline infusion); a moderate dose lidocaine-treated group (2 mg/kg bolus and 70 μg/kg/min infusion); and a high dose lidocaine-treated group (2 mg/kg bolus and 100 μg/kg/min infusion). After 10 min of infusion the left anterior descending and septal coronary arteries were occluded at their origins. Infusions continued until VF occurred or 30 min elapsed. Fourteen of 16 control dogs died in VF. Sixteen dogs received lidocaine. Of the 11 treated dogs maintaining lidocaine blood levels within the accepted therapeutic range (1.2 to 5.5 μg/ml), 6 survived ($p<.05$). Ten of these 11 received the moderate dose regimen. Five other dogs received the high dose regimen; all died, with blood levels ≥6.3 μg/ml at the time of death. Since it has been suggested that detrimental effects may result from low blood levels of lidocaine, VF threshold (VFT) was determined in 3 dogs given lidocaine to maintain blood levels ≤1.2 μg/ml. No reduction in VFT was found. We conclude that lidocaine, at blood levels ranging from 1.2 to 5.5 μg/ml, significantly reduces the incidence of VF occurring early after coronary occlusion and that no decrease in ventricular electrical stability occurs at lower blood levels. Administration of this agent therefore may be of particular value in the early phases of acute myocardial infarction.

THE EFFECT OF DIGITALIS ON SINOATRIAL CONDUCTION IN MAN

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Digitalis induced abnormalities of sinoatrial (SA) conduction are not recognized unless SA block is observed. The effect of digitalis on SA conduction has not been determined in man. A catheter advanced to the high right atrium was used to apply a premature atrial impulse after every eighth basic beat. When the premature beat is applied in the midzone of the basic cycle, analysis of the basic cycle interval and the interval from the atrial premature depolarization (APD) to the recovery beat allows computation of the sinoatrial conduction time (SACT). This interval represents the conduction time required for the impulse to travel to the SA node and return to the atrial recording catheter. Five normal patients were studied before and after ouabain (0.01 mg/kg). The SACT was prolonged after ouabain in all patients with an average change of 52.8 msec. The increase of the SACT correlated with the prolongation of atrioventricular conduction ($r = 0.92$). In two patients with sinus rhythym and digitalis induced SA block, application of APD's defined two separate groups of recovery intervals differing by one basic cycle length; this represented second degree SA block. This study defines a means of measuring sinoatrial conduction and demonstrates that digitalis prolongs SA conduction.

HEMODYNAMIC EFFECTS OF 1-ISOPROPYLAMINO-3-(2-THIAZOLOXY)-2-PROPANOL·HCl IN THE EXPERIMENTALLY INFARCTED DOG

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ITP (1-isopropylamino-3-(2-thiazoloxy)-2-propanol·HCl) is a selective myocardial β-stimulant with selective myocardial β-blocking activity which has previously been shown to increase (↑) myocardial contractility, cardiac output (CO), coronary blood flow, heart rate (HR); moderately decrease (↓) total peripheral resistance (TPR) and produce little or no effect on systemic blood pressure. We studied the effects of ITP (4 mg/kg, I.V. bolus), saline (0.1 cc/kg, I.V. bolus) and isoproterenol (0.1 μg/kg, I.V. infusion) administered to three groups of experimentally infarcted dogs. A 40-50% myocardial infarction of the left ventricle (LV) (measured by Evans Blue injection) was produced in each dog. Saline produced no significant hemodynamic effects. ITP produced significant ↑ in CO, 22%; LV dp/dt, 36%; stroke volume (SV), 21%; but produced no significant changes in aortic pressure, LV pressure or S-T segment elevation. TPR decreased. Isoproterenol produced greater increases in CO, SV, HR and a greater ↓ in TPR. Isoproterenol, however, appeared to ↑ S-T segment elevation to a significant degree. We conclude that ITP is effective in the treatment of myocardial failure in the dog and would seem a useful adjunct in the treatment of heart failure. Studies in humans are now underway.

SPORTS, DEATH, AND UNUSUAL HEART DISEASE

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The increasing number of deaths recorded in individuals engaged in professional, amateur and recreational athletics prompted the authors to investigate the cardiovascular risk inherent in such activities. The records of the A. F. I. P. were searched and over 11,000 autopsies from the Registries of Cardiovascular Pathology and Forensic Pathology were reviewed. Cases fulfilling the following criteria were selected for further study: (1) Sudden and unexpected death in an asymptomatic individual; (2) Death or symptoms occurring during physical exercise; (3) Survival of less than 24 hours; (4) Death or symptoms witnessed by a reliable observer; (5) An adequate autopsy protocol excluding other than a cardiac cause of death; (6) Subjects 40 years or over were excluded. These criteria yielded 113 cases with an average age of 21.6 years. Besides a distribution of deaths in the expected category (i.e., coronary artery disease, myocarditis), the more unusual cases included sickle cell heart disease, congenital coronary anomalies, cardiac sarcoid, and fibroelastosis. The clinical and pathological findings and distribution of cases are reviewed.

BENIGN PROGNOSIS OF RIGHT BUNDLE BRANCH BLOCK AND LEFT ANTERIOR HEMIBLOCK AFTER INTRACARDIAC REPAIR OF TETRALOGY OF FALLOT

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Right bundle branch block and left anterior hemiblock (RBBB & LAH) occurring after intracardiac repair of tetralogy of Fallot (TOF) has been accorded an ominous late prognosis with a high incidence of late onset complete heart block (CHB) and sudden death. We studied 141 survivors of intracardiac repair of TOF operated upon between 1958-72, to document the incidence of RBBB & LAH and to study the late prognosis. RBBB & LAH occurred in 31 (22%) all of whom have complete follow-up.Transient CHB occurred post-operatively in 2 patients; there were no other significant arrhythmias. Two late deaths have occurred, neither from arrhythmia (1 at attempted VSD reclosure, 1 of progressive congestive heart failure).The remainder are well an average of 76 months post-operatively (range 144-12 months).
The absence of late onset CHB or sudden death in this series contrasts with the relatively high incidence of these events in some studies of RBBB & LAH post intracardiac repair of TOF. However in these reports a history of transient postoperative CHB(indicative of trifasicular disease in this setting) can be found in the majority of those developing late onset CHB or sudden death. We conclude that RBBB & LAH occurring after intracardiac repair of TOF does not of itself carry a bad late prognosis. The critical parameter of bad late prognosis in patients with EKG evidence of RBBB & LAH may be the history of transient post-operative CHB.

DILATATION OF THE MITRAL ANULUS: A RARE CAUSE OF MITRAL REGURGITATION

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Many now believe that mitral anular dilatation is an infrequent cause of mitral regurgitation, but supportive studies for this belief are not available. To confirm or deny this concept, the mitral anulus was measured in patients with normal hearts and in patients with cardiac conditions associated with left ventricular dilatation with and without mitral regurgitation. The mitral anulus measured 8.0-10.5 (average [avg] 9.0) in 15 normal hearts, 9.0-12.0 (avg 11) in 20 hearts with primary myocardial disease, 9.0-13.0 (avg 11) in 10 hearts with pure mitral regurgitation due to abnormalities of leaflet or chordae tendineae, and 9.5-13.0 (avg 11) in 10 hearts with pure aortic regurgitation without mitral regurgitation. The mitral anulus in 3 patients with the Marfan syndrome without mitral regurgitation measured 8, 10, and 12 cm respectively, and in 3 patients with mitral regurgitation, 15, 15, and 17 cm. Although the mitral anulus was dilated about 20% greater than normal in patients with primary myocardial disease, and with pure aortic regurgitation and with pure mitral regurgitation, no difference in anular size between patients with and without mitral regurgitation was observed. Hence, mitral regurgitation in patients with left ventricular cavity dilatation is not due to mitral anular dilatation. An exception is the patients with the Marfan syndrome in which the mitral anulus associated with mitral regurgitation was nearly twice normal size, and also larger than in Marfan patients without mitral regurgitation. Thus, disease of the fibrous skeleton of the heart may be necessary for mitral anulus to dilate enough to cause mitral regurgitation.

EFFECTS OF NOREPINEPHRINE ON HIS ELECTROGRAMS IN THE DENERVATED HUMAN HEART

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The effects of norepinephrine (NE) on atrioventricular conduction determined with His bundle electrograms were studied in four patients one to three years after cardiac transplantation. Baseline A-H and H-V times were normal. NE, 4 to 8 μg/min, was infused to produce a rise in arterial pressure, while atrial donor rate, atrial recipient rate, A-H and H-V times were monitored. Concomitant with an average increase of 72 mm Hg in arterial pressure, atrial recipient rate slowed by an average of 23 beats/min, while the atrial donor rate increased by an average of 32 beats/min. The A-H interval decreased by an average of 27 msec; the H-V interval did not change. After propranolol (7 mg in two patients), NE infusion increased atrial donor rate by only 7 beats/min; A-H time did not change, but comparable increases in arterial pressure occurred. Our studies show: 1) the transplanted sinus and atrioventricular nodes are responsive to NE; 2) denervation hypersensitivity to NE was not seen; 3) the beta adrenergic effects of NE are blocked by propranolol, while the alpha effects are not; 4) the transplanted heart does not respond to reflex baroreceptor stimulation with increased arterial pressure, while the recipient atrium slows appropriately, demonstrating no evidence for reinnervation.

MANAGEMENT OF THE VENTRICULAR SEPTAL DEFECT IN TRANSPOSITION

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Forty-four patients who have undergone correction of Transposition of the Great Arteries complicated by Ventricular Septal Defect with or without pulmonary stenosis are reviewed. All except 13 were operated on with surface induced deep hypothermia and circulatory arrest. In 30 patients, the ventricular defect was closed through a right atriotomy, in 11 patients through a right ventriculotomy, and in two patients with muscular defect, through a left ventriculotomy. In one, the defect was closed through a pulmonary arteriotomy. The advantages of avoiding an incision in the systemic ventricle are emphasized.

Analysis of the results indicate that primary definitive repair of TGA with VSD and pulmonary artery hypertension is inferior (33% mortality) compared to early banding followed by early debanding and primary correction in the first year of life (0 mortality). Late debanding and correction carries a higher mortality and morbidity due to the technical difficulties associated with the band and the post-operative pulmonary problems due to extensive bronchopulmonary collaterals.

It is recommended that early banding should be followed by early debanding in this group in infancy and that the ventricular defect be closed without right ventriculotomy.

CLINICAL EXPERIENCE WITH AN IMPLANTED RECHARGEABLE TRANSVENOUS PACEMAKER

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Rechargeable battery powered fixed rate or demand pacemakers were implanted in 9 patients with symptomatic bradycardia, with or without heart block. The double hermetically sealed generator is 21% smaller and 27% lighter than any other available pacemaker, and is recharged by the patient using a portable external charging coil at home for 90 minutes weekly. A telemetry feedback loop confirms the charging current input to the implanted Ni-Cd batteries. In the event of a deficient charge, a gradual slowing in rate would be observed. The bipolar electrode readily screws without tools or adhesives into the generator casing providing 10,000 p.s.i. of electrode contact. These units continue to function normally after 2 years in dogs with experimental complete heart block and in 35 patient-months (longest implant 6 months) of clinical use. Three of the patients had prior experience with one or more conventional mercury battery generators and have stated a preference for the new unit. Rate and rhythm are monitored weekly by telephonic ECG transmission and no malfunction or decline in rate has been observed in any patient including one who did not charge the unit for 4 weeks.

The advantages of this pacemaker system include: (1) small size and light weight, (2) rapidly achieved secure electrode connection, and (3) anticipated function for over 10 years (based on accelerated in vivo testing).

DIPHENIDOL A NEW AGENT FOR THE TREATMENT OF DIGITALIS-INDUCED ARRHYTMIAS, IN MAN.

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Diphenidol, a new antiemetic agent, has been shown to be effective in treating arrhytmias secondary to digitalis intoxication, exerting it's action through a shortening of the prolonged A-H time, and suppressing the enhanced ventricular automaticity. In a group of 30 patients with varied cardio-vascular pathology, and digitalis-induced ventricular arrhytmias, Diphenidol was given in a dose of 0.5 mg/kg intravenously; in the 30 patients, the return to sinus rhythm occurred in 5 to 15 minutes after the administration of the drug. In 3 patients the arrhytmia returned 3 hours after the initial dose, and the return to sinus rhythm was acomplished through a second similar dose of Diphenidol, in 5 to 15 minutes. Hemodynamic studies in these patients corroborated that the administration of Diphenidol in a dose range of 0.5 to 8.0 mg/kg had no significant effect on: Cardiac Index (liters/min/m^2) Initial: 2.8, after 10': 2.6; Total Peripheral Resistance (dynes/sec/cm^{-5}) Initial: 1930, after 10': 2200; Mean Arterial Pressure (mm. Hg) Initial: 98, after 10': 96; Stroke Index (ml/beat/m2) Initial: 30.7, after 10': 32.7; Heart Rate (beats/min) Initial: 170, after 10': 135. Diphenidol showed a significant effect on shortening the A-H time (-25.6 $\pm$ 6 percent) already prolonged in the digitalis toxic state.

MULTIPURPOSE FLOTATION ELECTRODE CATHETER - A NEW CATHETER FOR ARRHYTHMIA AND INTRACARDIAC PRESSURE MONITORING

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A balloon tipped flotation catheter (5F) and two sets of platinum electrodes positioned at 11 and 12 cm, and 25 and 26 cm from the tip has been designed for recording intracavitary electrograms and monitoring pulmonary vascular pressures. The multipurpose flotation electrode catheter (MFEC) has been evaluated in 29 patients and the results demonstrate that: (1) The catheter can be passed easily at the bedside without fluoroscopy by monitoring either the intracavitary electrogram or the intracardiac pressure; (2) With the catheter tip stabilized in the pulmonary artery or its branches and measuring pulmonary artery pressure, the distal and proximal electrode pairs record simultaneously, right ventricular (RV) and right atrial (RA) bipolar electrograms, respectively. Such electrograms with appropriate filters (RV 15-300 Hz, RA 50-300 Hz), in contrast to surface electrocardiogram, do not show baseline shift, are virtually free of respiratory variation and artifacts due to patient movement and the signal to noise ratio is approximately 100:1; and (3) Reliable atrial pacing (threshold < 3 ma) was visible in the majority of patients. Ventricular pacing but at high threshold could be achieved in only a few patients. The catheter provides a simple means not only for monitoring intracardiac pressures but also for obtaining artifact free, clear, simultaneous RA and RV cavity electrograms for diagnosis of cardiac arrhythmias and suitable for online computer monitoring.

HEMODYNAMIC STUDIES OF SEQUENCED AND NON-SEQUENCED EXTERNAL COUNTERPULSATION

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External counterpulsation, using sequential (S) inflation of pressurized leg cuffs (first distally and then proximally), was compared to simultaneous non-sequenced (NS), inflation of the cuffs. Six patients were studied during diagnostic cardiac catheterization, four with documented coronary artery disease, two with normal coronary vessels.

Central aortic (Ao) and left ventricular pressures (mm.Hg.), and cardiac output (CO) in L/min., were measured in the control (C), non-sequenced, another control and sequenced states. Non-sequenced and sequenced were each compared to their own control measurements.

	HR	Syst. Ao.	Diast. Ao.	Peak Diast.Ao.	Mean Ao.	CO
C	69±4	118±5	72±2	80±3	90±4	4.8±.6
NS	69±4	115±8	73±4	108±5*	94±5	5.0±.4
C	68±3	116±6	72±3	80±3	89±4	4.8±.4
S	67±3	113±7	73±4	111±5*	96±4	5.5±.5**

*p < 0.0005 **p < 0.005

The rise in CO with non-sequenced pulsation was not significant (p < 0.4). The rise in CO with sequenced pulsation was significant (p < 0.005). Peak diastolic augmentation and left ventricular end-diastolic pressure was equivalent in both modes of counterpulsation. Sequential counterpulsation leads to a greater increase in CO than does non-sequenced, presumably through more efficient augmentation of venous return.

EFFECT OF CLOFIBRATE ON PROGRESSION OF CORONARY DISEASE: A PROSPECTIVE, ANGIOGRAPHIC STUDY IN MAN

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Lowering blood lipids has been invoked as a means of controlling future coronary events. In this prospective study, the effect of a lipid-reducing agent clofibrate (CL, 2g daily) on extent of coronary artery (CA) disease was investigated. Forty pts, 31 having aortocoronary bypass, 7 having Vineberg operations, 2 having neither, were placed double-blind in placebo (PL, 24 pts) and CL (16 pts) groups, and restudied by selective coronary angiography one year later. An additional 24 pts dropped from the study, due to adverse drug reactions in 6. Each pt's right, left, anterior descending, and circumflex CAs (with their branches) were separately rated according to degree of obstruction. The CL group showed a significantly greater fall in triglyceride than PL group (-13.7% vs +2.3%; P=.45). In the CL group, 19 of 64 CAs (29.6%) showed progressive coronary narrowing, not significantly different from the PL group (24 of 96 CAs, 25%, narrowed; P=.26). No significant differences between drug groups emerged when the data were corrected for degree of fall of blood lipids, initial lipoprotein type, or effect in bypassed vs nonbypassed vessels (P always > .2). Regression of CA disease was not seen. We conclude that CL did not significantly influence the rate of progression of coronary artery disease in a one-year period.

CORONARY STEAL: ROLE IN DETRIMENTAL EFFECT OF ISOPROTERENOL FOLLOWING ACUTE CORONARY OCCLUSION.

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Using epicardial electrograms others have established that Isoproterenol (Iso) infusion increases myocardial injury after acute coronary (cor) occlusion. To define the contribution of alterations in collateral blood flow to this increased ischemia, we have administered Iso to 10 dogs. After pretreatment with practolol in doses which successfully block inotropic but not vascular effects of β stimulants, intracoronary (IC) Iso continued to enhance the magnitude of S-T elevation in ischemic areas. Thus, vasodilation induced by Iso appears to divert flow from the ischemic area. To test this hypothesis IC adenosine (Ad) was given to cause cor vasodilation without enhancing inotropy. S-T elevation at ischemic and adjacent sites was significantly increased. Addition of IC Iso to the Ad infusion increased inotropy without further increasing cor flow, and was accompanied by evidence of greater myocardial ischemia. Neither agent had systemic effects, but each increased cor blood flow while concomitantly decreasing collateral flow as evidenced by a fall in cor pressure distal to the ligature and retrograde flow. In addition Ad significantly diminished the rate of ^{133}Xe clearance from the ischemic myocardium. Thus, Iso increases myocardial injury by two mechanisms. The observed increase is partly related to its positive inotropic effect. Moreover, cor steal itself also significantly aggravates ischemia by diminishing collateral blood flow to acutely ischemic myocardium. Intravenous Iso additionally diminishes collateral flow by decreasing cor perfusion pressure. It is postulated that any agent which causes either a primary or secondary cor vasodilation may cause a cor steal and subsequently enhance myocardial injury.

LOCALIZATION, DETECTION AND SIZING OF MYOCARDIAL INFARCTION WITH TECHNETIUM-99m-TETRACYCLINE AND ELECTROPHYSIOLOGIC TECHNIQUES

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Electrophysiologic data were correlated with Technetium-99m-Tetracycline (^{99m}Tc-TC) concentration and histopathology. Suction electrode recordings of monophasic action potentials (MAP's) and epicardial electrocardiography (EE) were used to map the location and site of myocardial infarction (MI). MI was produced in 18 mongrel dogs by external occlusion (EO) (11 animals) or embolization (EB) (7 animals). ^{99m}Tc-TC was injected IV 24 hr (EO) and 40 hr (EB) post-occlusion and studied 24 hr (EO) and 8 hr (EB) later. In normal areas the EE showed Rs complexes with inverted T waves. The MAP's had a normal configuration with an amplitude of 52 ± 6 mA. In infarcted areas EE showed QS, Qr, or 2-3 mm ST segment elevation. MAP's showed either an isoelectric line, an electrogram, or decreased amplitude (11 mA ± 5) with increased ratio of phase 0 to phase 2 amplitudes and a "hump" or prolongation of phase 3 repolarization. There was excellent correlation between MAP, EE, and ^{99m}Tc-TC concentration for sizing and locating the MI in 17/18 dogs. In 1 dog the ^{99m}Tc-TC concentrated in a small area of myocardium (1%) while electrophysiological studies were normal. In tissue samples taken from an area that appeared from ^{99m}Tc-TC and electrophysiological mapping to be infarcted, the electron microscopic examination also revealed an infarct. Microscopic examination showed small cellular areas of damage in two hearts that appeared normal by electrophysiological and isotopic studies. MAP's, EE, and ^{99m}Tc-TC mapping accurately size and localize areas of MI.

ECHOCARDIOGRAPHIC EXAMINATION OF THE ANTERIOR LEFT VENTRICULAR WALL IN PATIENTS WITH CORONARY ARTERY DISEASE.

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Previous studies have demonstrated segmental changes in the echocardiographic motion of the interventricular septum (IVS) and posterior left ventricular wall in coronary artery disease (CAD). Moving the transducer laterally 2-3 inches from where the mitral valve, right (RV) and left ventricles (LV) are recorded, the IVS is crossed and the anterior RV wall becomes the anterior left ventricular wall (ALV). The ALV was recorded in 50 of 54 consecutive patients having coronary arteriography. Twelve patients were normal and 42 had CAD ($\geq$ 50% obstruction). Abnormal ALV motion (flat or anterior motion during systole) was noted in 21 patients. Twenty of these patients had CAD, with 18 patients having left anterior descending artery (LAD) lesions. One patient had an isolated right coronary artery (RCA) obstruction, and one had a RCA and left circumflex lesion. In 14% of the patients with CAD (6 of 42), the ALV was the only area of the LV echogram which demonstrated abnormal motion. This echocardiographic technique offers the examination of another area of the LV which is frequently affected by CAD and should be particularly useful in patients with LAD lesions.

SUSTAINED LOSS OF MYOCARDIAL NOREPHINEPHRINE AFTER RELIEF OF CONGESTIVE HEART FAILURE

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It is not known if the depletion of cardiac norepinephrine (NE) stores which accompanies pressure overload hypertrophy and congestive heart failure (CHF) is reversed following relief of CHF. Right (RV) and left (LV) ventricular NE stores were evaluated in 3 groups of cats:4 controls, (C); 5 with CHF due to 13 days of pulmonary constriction, (F); and 5 studied 32 days after relief of a 13 day period of CHF due to pulmonary constriction, (R).

	Control	CHF	Recovery
Heart rate, beats/min	234±13	196±16	234±13
Cardiac output/ml/min/Kg	68.9±.23	47.9±1.0	72.8±2.2
Systolic pressure mmHg	199±10	154±7	180±9
Diastolic pressure mmHg	150±7	115±7	139±7
RV systolic pressure mmHg	36.1±2.5	77.1±4	32±3.3
RV end diastolic pressure	3.25±2.5	14.9±1.4	2.58±57

RV wieght increased from C=0.52±4g/Kg to F=1.14±.08 ($p<0.01$) and following relief did not recover (R= 0.78±.08). LV weight remained relatively constant (C= 2.06±.15g/Kg,F=2.4±.08,R=2.56±21,p 0.1). NE was reduced from the control value of 1.42±29ug/g (RV) and 1.35±.33 (LV) to 0.08±.02 (RV) and 0.72±.08 (LV) in F, and remaind low in R,0.27±.09 (RV) and 0.63±.12 (LV) despite relief of CHF. Thus the cardiac adrenergic defect of congestive heart failure is not relieved by abolition of the pressure overload and resultant hemodynamic abnormalities. Further, it is suggested that, the persistence of NE depletion does not result from hypertrophic structural changes since reduced catecholamine levels continued in the left ventricle which did not hypertrophy.

HEMODYNAMICS AND MYOCARDIAL METABOLISM ABNORMALITIES IN FRIEDREICH'S ATAXIA

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Nine patients (pts), 9 to 40 yrs old (average 22 yrs) suffering from Friedreich's Ataxia (F.A.) were studied during right and left heart catheterization and had left ventricular angiograms. Coronary sinus and arterial determinations of lactate were performed at rest in 7 pts and also during pacing in 6 pts. At rest, a left intraventricular systolic gradient (V.S.G.) was noted in 1 pt (78mmHg). 5 pts were also studied during isoproterenol infusion: a right V.S.G. appeared in all 5 pts (range 12-28mmHg) and a left V.S.G. in 2 pts (20 and 22mmHg). The end diastolic volume index was 48.9 ml/M^2 (range 28.8 - 75.5) and ejection fraction 77.7% (range 49-90%). L.V.E.D.P. was 15.1mmHg ±2.2 at rest, did not change significantly during pacing 13.2mmHg ±4.8 but was 20.5mmHg ±5.3 ($P<0.025$) after left ventricular angiography. Left ventricular stroke work index was 35.5Kgm/beat/M^2 ±8.2 at rest and 18.5 ±8.5 ($P<0.01$) during pacing. The mean rate of circumferential fiber shortening ranged from 0.6 to 3.1 circ./sec. The mean myocardial lactate extraction was 34.5% ±12 at rest (with less than 10% extraction in only one pt) and 16.8% ±14.1 ($P<0.025$) during pacing (with production in 4 of 6 pts). The mean O_2 extraction was 47% ±11 at rest and decreased to 30% ±13 ($P<0.01$) during pacing. The hemoglobin-O_2 dissociation curve was shifted to the left in 5 of 8 pts (P50 range 22.5 - 25 mmHg). The angiograms of all these pts demonstrated the hypertrophic nature of the cardiomyopathy in F.A. with or without significant outflow obstruction. 5 of 7 pts, either at rest or during pacing, had evidence of myocardial anaerobic metabolism associated with an increased hemoglobin affinity for O_2 and an abnormally low myocardial O_2 extraction.

COMPARATIVE EFFECTIVENESS OF EXERCISE TESTING AND HOLTER MONITORING FOR DETECTING ARRHYTHMIAS IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

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To detect arrhythmias requiring therapy, we studied 50 patients (pts) three to 44 months following myocardial infarction by both submaximal treadmill exercise testing (TE) and 10 hours of continuous ECG monitoring (HM) during normal activity. Fourteen pts (28%) had an enlarged left heart dimension on ECG-triggered x-ray ($>52mm/M^2$). In 23 pts (46%) significant arrhythmias were detected (ventricular tachycardia, atrial tachyarrhythmias, $>$ 2 PVCs/min on TE or $\geq$ 1 PVC/500 cycles on HM). Fourteen pts (28%) had frequent ectopic beats during or within 15 minutes after TE and 18 pts (36%) had significant arrhythmias during HM. In nine pts (18%) HM detected significant arrhythmias when TE did not, while in five instances (10%) frequent PVCs were present with TE but not during HM. In five of nine pts in whom both tests were positive, HM detected serious arrhythmias such as ventricular tachycardia when TE showed only isolated PVCs. Eight pts (16%) had one or more PVCs on resting ECG and all had significant arrhythmias detected by TE and/or HM; five pts were in NYHA Class III and all had significant arrhythmias. The presence of arrhythmias did not correlate with patient age, history of palpitation, left heart dimension, duration of follow-up, site of infarction by ECG, or development of angina or ST depression during TE. We conclude that both TE and HM are required for complete arrhythmia detection in post myocardial infarction pts and that HM often discloses different and more serious arrhythmias than TE.

DISSECTION OF THORACIC AORTA:MEDICAL OR SURGICAL THERAPY?

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In a 10 year period, at the Peter Bent Brigham Hospital (1963-1973) dissection of the thoracic aorta was diagnosed by aortography, surgery, or postmortem examination in 45 patients (pts). Indications for surgical or medical therapy varied during this decade reflecting the shifting therapeutic concepts of this period. The pts were reviewed to assess the results of therapy (Rx) and to critically reassess the indications for surgery in this disease.

Dissection originated in the ascending aorta (DAA) in 31 pts. Twenty-one of these pts had primary surgical Rx; 16 (76%) survived; 12(57%) were alive and well (A/W) at follow-up. Of 10 pts with DAA who did not have surgical Rx, 3 (30%) survived and only 1(10%) was A/W at follow-up. Of 14 pts with dissection of the descending aorta (DDA), primary Rx was medical in all 14, and was successful in 6(43%) who were A/W at follow-up. In 8 pts DDA progressed despite medical Rx and surgery was required. Only 2(25%) of these pts survived.

Analysis of all cases revealed that at the time of admission 21(68%) of the 31 pts with DAA had one or more of the following absolute contraindications to medical Rx: hemopericardium (9), new AI with CHF (10), jeopardized carotid or coronary arteries (4) or systolic pressure<120 mm Hg with documented prior hypertension (4). However, no pt with DDA had a contraindication to medical Rx at the time of admission.

Thus, in a 10 year period at this hospital medical Rx was contraindicated in 21 of 31 pts with DAA, and was unsuccessful in 8 of 10 pts in whom medical Rx was even feasible. We conclude that the appropriate Rx for DAA is surgical. In pts with DDA, medical Rx is usually feasible and at times successful.

IDENTIFICATION OF CRITICAL CORONARY ARTERY LESIONS BY SUBMAXIMAL EXERCISE TESTING

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Increased mortality rates in patients with coronary artery disease (CAD) have been associated with both the magnitude of ST segment depression in post-exercise electrocardiograms and the presence of certain severe obstructive lesions, e.g. in the main left coronary artery (MLCA) or proximal left anterior descending (LAD) artery. In an attempt to identify the subgroup of CAD patients who have critical lesions, all patients who had 2 mm or more ischemic ST depression (ISD) on standard treadmill tests and who had coronary arteriography were evaluated. 37 patients met these criteria. 9/37(24.3%) patients had MLCA lesions 75% or more of the lumen diameter. Another 9/37(24.3%) had the equivalent of MLCA lesions, i.e. 75% or greater in both LAD and left circumflex (LCx) arteries proximal to any branches. Another 9/37(24.3%) patients had 75% or greater occlusion of the LAD proximal to the first major branch. Thus, of patients with 2 mm or more ISD on treadmill testing 18/37 (48.6%) had either critical MLCA or MLCA equivalent lesions and a total of 27/37(73%) had critical lesions. 22/27(81%) patients with critical lesions were considered operable on the basis of favorable anatomy. The magnitude of ST segment depression did not correlate with the severity of angina pectoris. Our data suggest that ISD 2 mm or greater indicates a high probability of critical coronary lesions. These patients should be considered for coronary arteriography in order to identify critical lesions that are potentially amenable to bypass surgery.

ANTIARRHYTHMIC EFFECTIVENESS OF 17,21-DI-MONOCHLORO-ACETYL-AJMALINE: HEMODYNAMIC AND METABOLIC STUDY

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A study was designed to evaluate the antiarrhythmic effectiveness of 17,21-di-monochloroacetyl-ajmaline (DCAA).

Twenty dogs which received a digitoxic dose of 0.15 mg/Kg (I.V.) exhibited serious arrhythmias leading to a mortality of 60% (LD_{60}). Ten other dogs were treated with DCAA (1.74 mg/Kg) following digoxin LD_{60}. Serious digitalis-induced arrhythmias were abolished by DCAA in eight out of the ten dogs. Treatment decreased the mortality rate to 20%.

In another series of dogs, hemodynamic and metabolic function were measured prior to and following digitalis LD_{60}, and after administration of DCAA. Digitalis-induced tachyaarhythmias were accompanied by a reduction in systemic pressure, cardiac output and stroke work; abnormal myocardial lactate metabolism; and significant potassium loss. His bundle recordings revealed abnormal A-V conduction. Administration of DCAA usually converted the arrhythmias and normal A-V conduction usually was restored. Hemodynamic and metabolic studies revealed DCAA did not depress cardiac function. Coronary sinus flow increased after DCAA. Metabolic measurements revealed improved myocardial lactate balance and reduced oxygen extraction, but potassium balance remained unchanged. DCAA is an effective antiarrhythmic agent. It significantly reduced digitalis LD_{60} mortality rate and did not depress myocardial function.

COFFEE AND CORONARY HEART DISEASE

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A study was conducted utilizing the data from 18 years of follow-up in the Framingham Study to determine the relationship between coffee consumption and coronary heart disease (CHD). Coffee consumption was determined at the fourth biennial examination. A follow-up period of 12 years permitted a study of the relationship between coffee consumption (from none to 7+ cups per day) and the subsequent development of CHD. The association between coffee consumption and other risk factors, including cigarette smoking, was also investigated. Coffee consumption was studied in relation to: total CHD, angina pectoris, myocardial infarction, sudden death, other deaths from CHD, and death from all causes. No statistically significant relationship was found between coffee intake and these clinical categories except for "death from all causes" in which an increase in risk was observed with increasing coffee consumption. Further study showed that this relationship could be accounted for by the association between coffee consumption and cigarette smoking. It was concluded that coffee consumption, as engaged in by the general population, is not a factor in the development of CHD nor any of its manifestations.

CORONARY VENOUS INOSINE AS A METABOLIC INDICATOR OF MYOCARDIAL ISCHEMIA

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During regional ischemia (Isch) changes in concentration of coronary vein inosine (I) and hypoxanthine (HY), catabolites of adenosine, and lactate (L) and potassium (K) were compared in 14 open-chest pigs. A fixed decrease in coronary blood flow from 46 ± 5 (SE) ml/min to 13 ± 2 ml/min was produced with a screw clamp and flow probe around the left anterior coronary artery. Regional venous blood was obtained from a local anterior coronary vein simultaneously with arterial samples. The mean of 3 serial 2-min values of I, HY, L and K during a control and Isch period were compared. During Isch, I increased from 10.9 ± 0.7 μM to 18.5 ± 1.8 μM ($P<0.001$); HY increased from 29.2 ± 1.5 μM to 33.0 ± 1.5 μM ($P<0.05$). Mean concentration of K and L and arterial concentration of all the substances did not change significantly. Within 2 min of Isch, however, K increased from 3.77 ± 0.10 mM to 4.16 ± 0.14 mM ($P<0.05$), but fell to control levels at 4 and 6 min. Percent L extraction changed from 42.6 ± 6.7% to -4.6 ± 12.5% ($P<0.005$) during Isch. These data indicate that I and HY concentration increases in the venous effluent of the Isch myocardium associated with changes in percent L extraction. Of the four compounds studied I is the most sensitive indicator of myocardial Isch.

THE SHORT-TERM PROGNOSTIC VALUE OF H-V INTERVAL IN PATIENTS WITH BIFASCICULAR BLOCK

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Electrophysiological studies have been performed in 119 adults with chronic right bundle branch block and left axis deviation (-30° to -180°). H-V interval (normal 35-55 msec) was normal in 86 patients (NHV) and prolonged in 33 (PHV). PHV and NHV patients did not differ significantly in regard to age or sex. The following clinical variables were more frequent ($P<0.05$) in patients with PHV: Cardiac third sound (PHV vs NHV) 8/33 (24%) vs 5/86 (6%), holosystolic murmurs 12/33 (36%) vs 11/86 (13%), cardiomegaly on X-ray 24/33 (73%) vs 41/86 (49%), congestive heart failure 16/33 (48%) vs 19/86 (22%), and functional class (NYHA) III or IV 9/33 (27%) vs 3/86 (3%). All patients were prospectively followed in a conduction clinic at one to two monthly intervals after initial electrophysiological evaluation. Mean duration of follow-up was 279 ± 39 days in PHV patients and 316 ± 30 days in NHV patients. Documented second or third degree block distal to H developed in only 2 patients (1 PHV and 1 NHV). Mortality was analyzed using life table methods. One and two year cumulative survival in the PHV group was respectively 83.6% and 61.3% as compared to 85.8% and 81.3% in the NHV patients. The higher mortality ($P<.01$) at two years in the PHV patients primarily reflected progression of myocardial disease and not sudden death. In summary, prolonged H-V interval in patients with bifascicular block was often associated with serious myocardial dysfunction and a high mortality. The risk of progression of conduction disease was slight in bifascicular block patients with either PHV or NHV, during this relatively short follow-up period.

SURVIVAL IN LEFT MAIN CORONARY ARTERY DISEASE: THE ROLE OF CORONARY ANGIOGRAPHY, COEXISTING CORONARY ARTERY DISEASE, AND REVASCULARIZATION

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The assumption that left main coronary artery (LMCA) stenosis is the lethal factor in patients (pts) in whom it occurs has not been scrutinized. The role of direct revascularization (DR), the risk of coronary arteriography (CA) and the relative merits of different techniques of CA have been incompletely elucidated in these pts. Among 2100 pts studied by Judkins' technique (JT) there were 20 with 50 to 70% and 28 with 71 to 95% narrowing of LMCA luminal diameter. One death occurred 3 days after CA. No clinical parameter allowed reliable prediction of LMCA disease. Coexisting disease was found in 3 vessels in 21 pts, in 2 vessels in 16, in 1 vessel in 9, and in no other vessel in 2. Six of 10 pts judged inoperable by current criteria were dead within 16 months (mos). Of 16 patients judged operable, in retrospect, but treated without surgery, 8 were dead within 18 months (mos). The remaining 8 have survived 5 to 69 mos (mean 41 mos). There were one operative death and 2 late deaths among 16 pts treated with DR since 1970. While non-surgical survivors were functionally unchanged, each survivor in the DR group improved. Survival was not related to the severity of LMCA stenosis in any group.

We conclude that pts with LMCA disease cannot be identified before angiography but can be studied at low risk with JT. Prognosis in LMCA disease resembles that reported in 3 vessel disease alone. Analysis of angiographic data, including sequential angiograms in 15 pts, indicates that the major determinant of the poor prognosis in LMCA disease is the amount of coexisting disease. The extent of distal disease precludes surgery in 20% of pts but DR offers symptomatic benefit and may prolong life in the remainder.

FACTORS PREDISPOSING TO VENTRICULAR TACHYCARDIA IN ACUTE MYOCARDIAL INFARCTION

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In experimental myocardial infarction (MI), factors predisposing to ventricular tachycardia (VT) include frequent premature ventricular contractions (PVC's) and the R on T phenomenon. The purpose of this study was to identify the features associated with VT in acute MI in man. Twenty-four hour Holter monitoring was performed within 24 hours of the acute MI in 35 consecutive patients with measurement of: (1) incidence of VT (3 or more PVC's at a rate > 100 beats per minute), (2) total number of PVC's per 1000 normal beats, (3) coupling interval (CI) of beats initiating VT versus CI of PVC's in patients without VT, (4) prematurity index (PI) (coupling interval divided by QT interval of sinus beat), and (5) incidence of slow VT (<100 beats per minute). Seventy-one episodes of VT were documented in 18 patients; 17 patients had no VT. There was no significant difference in the anti-arrhythmic therapy of the two groups. Results are shown below.

	Mean CI (SEC)		Mean PI		Slow VT ($P<0.01$)
VT	0.61 ± 0.16	NS	1.50 ± 0.31	NS	10/18 patients
No VT	0.55 ± 0.15		1.46 ± 0.30		2/15 patients

The median number of PVC's in the VT group (5.1 per 1000 normal beats) was significantly greater than that in the group without VT (0.8 per 1000 normal beats); $P<0.01$. Contrary to previous reports the results show that the R on T phenomenon as measured by the CI and PI does not predict the occurrence of VT in acute MI. An increased frequency of PVC's and slow ventricular rhythms are clearly associated with an increased incidence of VT. These results demonstrate significant differences between the occurrence of VT in human MI and previous data obtained from experimental animals.

TRICUSPID ATRESIA: THE CLINICAL COURSE IN 96 PATIENTS. Macdonald Dick, M.D., Donald C. Fyler, M.D., Alexander S. Nadas, M.D., Children's Hospital Medical Center, Boston, MA.

The charts, electrocardiograms, catheterizations and angiographic data were reviewed in 96 patients with tricuspid atresia(TA); 46% (45/96) were female; 54% (57/96) were male; 38%(37/96) died in the first year of life; 4% (4/96) survived into the third decade. TA segregates into two therapeutic groups. Group A: TA with decreased pulmonary blood flow(↓PBF), accounting for 80%(77/90) of all TA. Type I TA(normally related great arteries) comprised 76% (59/77) of this group; 83% (49/59) received arterial shunts; 32%(16/59) died; 11%(7/59) received Glenn (G) anastomoses; 4/7 died; 16%(8/49) of the arterial shunts developed either congestive heart failure(CHF)(5) or pulmonary vascular obstruction(PVO)(3). However 16%(10/59) were not operated and all died. Type II TA (d-transposition of the great arteries) contained 16%(13/77) of this group; 7/13 received either arterial or venous shunts; 3/7 died (arterial shunts); 6/13 were not operated and all died. Type III TA (l-transposition of the great arteries) made up 6%(5/77) of this group; 4 received arterial shunts with 1 survivor. Group B: TA with increased (↑) PBF accounted for 20%(19/96) of patients with TA. Type I TA contributed 31%(6/19) to this group; all but one are alive (age 9 months-29 years). Type II TA contributed 53%(10/19) of this group; 5/10 developed pulmonary artery hypertension (PAH), 3/10 developed PAH with PVO. Type III TA made up 16%(3/19) of this group; 3 died in late adolescence all in CHF. Atrial arrhythmias (AA) developed in 7%(9/96) of patients; the arrhythmias were related to 1. catheterization(1), 2. L-TGA(3), and long standing CHF(3). None were lethal. This experience with TA indicates that surgical intervention in Group A, though necessary, has a high initial mortality(37%) and that those successfully shunted have a pattern of complications similar to Group B (CHF, PAH, PVO, AA).

INCREASED LONGEVITY WITH LOW OUTPUT (PROGRAMMABLE) PACEMAKERS - Doris J. W. Escher, MD,FACC; Seymour Furman, MD,FACC; Philip Hurzeler, Ph.D.; Montefiore Hospital and Medical Center, Bronx, NY.

In 14 months 61 Cordis Omnicor pulse generators (PG), 17 asynchronous (VA), 1 atrial (AS), 11 ventricular synchronous(VS), 32 ventricular inhibited (VI), have been implanted; 27 with new continuous coil electrodes (CCE) (0.08cm^2tip) and 36 on old electrodes-6 CCE, 12 2mm (2ME) (0.12cm^2tip), 15 4mm (4ME) (0.28cm^2tip) and 3 myocardial. The PG are noninvasively programmable to nominal rates (R) of 60, 65, 70, 80, 90, and 100 bpm (VS and AS to 80 only) and currents of 9(high), 6(med), 4(low) and 2.3 (test) mA by coded electromagnetic signals. With CCE, 2ME and 4ME at acute thresholds at approximately 0.4, 0.6 and 1.2mA respectively and chronic thresholds at 1.0, 1.5 and 2.2mA at 1msec pulses, all but 5 patients paced at test, 3 with new CCE but recent myocardial infarctions and 2 with old 4ME. Patients undergoing PG changes can be programmed immediately on the basis of twice the chronic threshold. New implants can be carried at low, medium or high for 1 month, and then programmed to low or test depending on anticipated threshold and programming trials. So far, 100% of our patients appear capable of being paced at low and 90% could be carried at test with a twofold margin of safety. This low threshold system allows temporary current increases post-implantation or injury with low later current drain and anticipation of 3 to 5 years of longevity, particularly with the VI where chronic current drain is only 6μA during total inhibition. Slower rates allow emergence of conducted rhythm and higher rates aid suppression of intruded beats. There have been 4 premature failures under 1 year - cause yet unknown.

THE EVOLUTION OF SECOND DEGREE BLOCK IN THE CANINE PROXIMAL HIS-PURKINJE SYSTEM

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Second degree block (2^o) was studied in 36 anesthetized dogs with acute ischemia of the proximal His-Purkinje system (HPS) due to ligation of the anterior septal artery. Using recordings from the His bundle (Hb) and both bundle branches (BB), the block was localized in the Hb in 26 and in the proximal BB in 10. An increase of the H-V time from 30±5 to 46±4 msec occurred before 2^o block developed. The first stage of 2^o block was a Mobitz type II (Mob II) block in which beats preceding and following the blocked impulse showed a "constant" H-V interval (within the measurement error). In 28 dogs stage 1 merged into stage 2 of 2^o block with gradual increment of the H-V interval before block (Wenckebach arrangement-WA). The increment can gradually increase from a few msec up to 180 msec. In 20 dogs this stage advanced to complete (3^o) A-V block. In 10 dogs the heart was excised and the portion of the septum containing the Hb and BB were superfused and probed with intra- and extracellular electrodes. Purkinje cells in the Hb and very proximal BB displayed a time-dependent block on pacing with progressive conduction delay before failure of impulse transmission. The Hb-BB conduction time before and after the blocked impulse varied from 5 to 120 msec. Characteristic changes in action potentials with slow foot potentials and hump-like prolongation of the plateau were observed according to the state of transmission and site of maximum conduction delay. We conclude: 1) ischemic HPS conducts decrementally and reflects mainly time-dependent kinetics in contrast to the voltage-dependent kinetics of normal HPS; 2) Mobitz type II and WA are different stages of the same electrophysiological disturbance with Mob II representing the initial stages of decrement of conduction.

ECHOCARDIOGRAPHIC FEATURES OF ENDOCARDIAL CUSHION DEFECT

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Five patients with endocardial cushion defect (ECD) were studied by echocardiography to establish the precise characteristics of their ultrasonic waveforms. Diagnosis was confirmed at surgery and/or by angiocardiography in 4 patients. Clinical, ECG, and X-ray findings were compatible with ECD in the other patient. The reproducible echo waveforms for each patient demonstrate the following features of ECD:

1. Multiple echo deformities in late diastole and early systole and a "break" in upstroke of mitral valve echo represent the cleft of the anterior leaflet of the mitral valve.
2. Rapid slope and large excursion of the mitral valve echo and large "v" waves of the posterior left atrial wall denote mitral insufficiency.
3. Paradoxical motion of the interventricular septum (IVS) with late systolic anterior motion of mitral echo indicate right ventricular diastolic overloading.

The study was repeated in one pt. postoperatively. All abnormal features of the echo waveforms were normalized except the paradoxical motion of the IVS. One pt. was studied six years after surgical closure of a primum ASD and suture of a cleft mitral valve. Echo deformities suggesting a cleft mitral valve and valvular insufficiency were present. Severe mitral regurgitation and a cleft mitral valve were found on selective left ventriculography confirming the postoperative breakdown of his mitral valvular repair as indicated by echo.

This study identifies the echocardiographic features of ECD and their value as an adjunct in clinical diagnosis and postoperative assessment.

THE VALUE OF HOLTER MONITORING IN ASSESSMENT OF CARDIAC ARRHYTHMIAS IN SYMPTOMATIC PATIENTS

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Thirty consecutive patients(pts) with dizziness, palpitations, syncope and multiple ECG's non-diagnostic for arrhythmias were monitored for 24 hours. There were 13 males and 17 females. Ages ranged from 27-83 years (mean 62). Pts were divided into 2 groups. Group I- In 14 pts (47%) no dysrhythmias were recorded. The etiology of cardiac disease was: ASHD (myocardial infarction or angina pectoris) in 8; RHD in 2; no known cardiac disease in 2; congenital heart disease in 1; and cor pulmonale in 1. Group II- 16 pts (53%) had abnormal recordings. Etiology of cardiac disease was: ASHD in 8; RHD in 2; no known cardiac disease in 5; myocardiopathy in 1. Holter monitoring revealed sinus bradycardia(SB)(34-54 beats/min) in 8 pts (50%). Sinus arrest (2.5,1.6,3.0, and 4.0 sec.) with junctional escape beats were present in 4 pts (25%). One patient in this group with sinus arrest of 3 sec. had SB at a rate of 36 beats/min and one episode of Wenckebach phenomenon. Three pts had a bradycardia-tachycardia syndrome. Two had chronic atrial fibrillation with a rapid ventricular response of 140 and 160 beats/min changing to 33 and 40 beats/min respectively. The third pt had paroxysmal atrial flutter (150 beats/min) alternating with SB at a rate of 40 beats/min. The remaining pt had a permanent demand pacemaker implanted for complete heart block who was hospitalized for syncope with no evidence of pacemaker malfunction; monitoring disclosed pacemaker failure with 4 sec. periods of cardiac arrest.

Sick sinus node was present in 15 of 16 pts with abnormal recordings. Twenty-four hour Holter monitoring is a very useful diagnostic tool in evaluation of symptomatic pts with paroxysmal dysrhythmias, however, a longer monitoring interval may be needed in those with non-diagnostic recordings.

FABRIC DEGENERATION IN STARR-EDWARDS CLOTH-COVERED HEART VALVE PROSTHESES

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Over the past three years, a series of 166 patients underwent either aortic or mitral, or a combination of aortic and mitral valve replacement, using the cloth-covered 2320 model aortic valve prosthesis and the 6320 model mitral valve prosthesis. Over the past 6 months there has been a very significant complication rate directly associated with degeneration of the fabric on these valves. Five patients were reoperated and their prostheses replaced with tissue valves. All 5 were noted to have significant fabric wear at the struts and also at the base of the sewing ring. Wear in general was extensive, with examples of total strut cloth dehiscence and severe deterioration at the composite seat. The sixth patient, a double valve replacement, had multiple myocardial infarctions which were eventually fatal. At postmortem they proved to be secondary to platelet fibrin aggregates originating from the frayed fabric on these valves. The total operative mortality was 9%. The mean 18 month mortality was 16% for aortic, 20% for mitral, and 47% for double valve replacement. A series of 50 homograft valve replacements over this same time interval had a 4% mortality rate. The 18 month mortality for a series of 369 patients using non-cloth-covered Starr-Edwards valves was 18%. The total 18 month embolic rate for the cloth-covered valves was 6% without long-term anticoagulation. Because of the high incidence of failure, we have discontinued the use of the cloth-covered valves. Patients with these valves should be continued on anticoagulation. Multiple embolic episodes should be treated by replacement with non-cloth-covered mechanical valves or with tissue valves.

STUDIES ON VENTRICULAR DEFIBRILLATION

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The role of a critical myocardial mass required to maintain ventricular fibrillation (VF) initiated by rapid ventricular pacing was studied by 2 methods in dogs placed on total cardiopulmonary bypass. Electrograms were recorded from atrium and from multiple sites on left (LV) and right (RV) ventricles. In the first method, the left circumflex (LC), left anterior descending (LAD) and right coronary (RC) arteries were cannulated with small polyethylene tubing which did not occlude blood flow. Injection of 1.0 to 1.5 mEq KCl simultaneously into LC and LAD abolished electrical activity over nearly the entire LV. VF in RV then regularized, spontaneously ceased and could not be reinitiated as long as LV was inexcitable. Injection of the same amount of KCl into RC failed to abolish VF in LV. Thus, when KCl depolarized LV, VF in RV could not be sustained but depolarizing RV did not terminate VF in LV. In the second method, pairs of circular electrodes (area=3.14cm^2) were sewn on RV and LV 4cm apart, parallel to the septum. We evaluated the amount of current necessary to terminate VF when passed in the form of a trapezoidal wave (24 msec duration) between the 2 RV electrodes, between the 2 LV electrodes, and between one RV and one LV electrode. The shock delivered between electrodes at opposite poles across both ventricles required the least current to terminate VF, while the shock delivered between 2 RV electrodes required the most. We conclude that successful defibrillation results when a critical myocardial mass becomes depolarized by either KCl or electrical discharge; depolarization of every cell in both ventricles is not necessary to terminate VF in the entire heart.

THE ACCURACY OF THE CONTINUOUS ECHOCARDIOGRAPHIC RECORDING METHOD FOR ASSESSING AORTIC ROOT SIZE

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To evaluate the normal range and accuracy of echocardiographic measurements of the aortic root diameter, we studied 109 patients without aortic valve disease or hypertension utilizing the continuous recording technique. The aortic root internal diameter was measured at end diastole in all patients. An additional 22 patients who underwent aortic valve replacement were also studied and the echo results were compared with the aortic annulus size measured at operation. The 109 normal patients consisted of 59 females and 50 males with an age range of 18 to 74 years (average 38 years). In these patients the echo root diameters ranged from 17 to 33 mm (mean 24 mm) with a mean diameter in females of 22.9 $\pm$ 3.6 mm compared to a mean diameter in males of 25.4 $\pm$ 3.3 mm which is a significant difference ($p < .0003$). This difference between males and females is not explained by body surface area. In the 22 operated patients the internal aortic root diameter measured by ultrasound averaged 26.7 $\pm$ 3.0 mm and the aortic annulus diameter at operation averaged 25.8 $\pm$ 1.5 mm. 16 of the 22 patients (73%) had root measurements by echo within 2 mm of the corresponding annulus size at surgery. The results in the 109 unoperated patients indicate a lower normal range of aortic root diameters than those previously reported in normal patients using the Polaroid film technique. Moreover, the measurements obtained in the 22 operated patients confirm the accuracy of the continuous echocardiographic recording method for assessing aortic root size.

LATE RESULTS OF THE BAFFLE REPAIR FOR TRANSPOSITION OF THE GREAT ARTERIES

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Fourteen unselected patients have been assessed hemodynamically 4 to 10 years (mean 5.5 years) after the Mustard operation for transposition of the great arteries (TGA). Investigations were directed principally at, i) detection of baffle obstruction by pressure measurements in the pulmonary veins (PV) and venae cavae and by recording simultaneously right ventricular (RV) and pulmonary wedge (PCW) pressures; ii) detection of baffle leaks by dye curves and by selective angiography; iii) assessment of RV and LV function by calculating peak VCE (dp/dt/28 p) from high fidelity recordings in 11 patients. Severe baffle obstruction to the PV return was found in 1 patient. The others had no or minimal gradients between the RV end-diastolic and PCW pressures (mean 1.3 $\pm$ 0.69 mm Hg). After Isuprel infusion cardiac output rose from 4.1 $\pm$ .22 to 7.1 $\pm$ .62 l/min/m^2 (+73%), but the gradient between RV end-diastolic and PCW pressures remained insignificant (2.2 $\pm$ 1.13 mm Hg). There was no caval obstruction. Baffle leaks were found in 5 patients with mild bi-directional shunting. Mild tricuspid regurgitation was demonstrated in 2 patients by RV angiography and was absent in 12 others. The contractility index peak VCE averaged 1.87 $\pm$ .122 sec^{-1} for the RV and was significantly lower for the LV (1.53 $\pm$ .135 sec^{-1}, $P < 0.01$). Only 1 patient presented significantly decreased contractility with a peak VCE of 1.07 sec^{-1} and poor contractility on the RV angiogram. These data indicate that the longterm outlook after the Mustard operation should be optimistic in most patients and that the RV is able to function at the level of contractility of a normal LV.

PLATELET AGGREGATION IN ANGINA PECTORIS: EFFECT OF EXERCISE INDUCED STRESS

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Several observers have suggested that platelet dysfunction may be important in the pathogenesis of symptomatic coronary artery disease. Platelet aggregates have been demonstrated in the coronary microvasculature of animal models following catecholamine infusions or the production of severe stress. To test the hypothesis that stress may lead to altered platelet function in man, exercise tolerance tests (ETT) were performed on 10 patients (pts) with angina pectoris and 10 age matched normals (nls) using a bicycle ergometer. Six angina pts had repeat ETT while receiving 80mg/day of oral propranolol (P). Exercise endpoint was either chest pain, severe fatigue or a heart rate of 160/min. Platelet aggregation (agg) studies were obtained at rest and immediately after exercise. Biphasic agg threshold in response to ADP and epinephrine was measured in fresh platelet rich plasma. At rest, minimum concentration of ADP for full agg response was 2.7± 0.6 uM in pts and 6.0±1.4 in nls ($p < .05$); with epinephrine, 8.6±3.1 uM in pts and 20±4.6 uM in nls ($p < .05$). However, following exercise with significant increase in heart rate and blood pressure, no change in agg threshold was found in either the nl or pt groups. At rest, P treated pts required an increased concentration of ADP to induce agg, 4.5±0.5 uM ($p < .01$); after exercise, this effect was maintained or further increased concomitant with improvement in work performance. Thus, exercise induced stress does not acutely alter resting platelet agg in nls or pts with angina pectoris. Angina pts show increased platelet agg at rest which is restored towards normal by P, an effect which persists despite submaximal exercise.

NON-INVASIVE ASSESSMENT OF CLINICAL RESPONSE TO ORAL PROPRANOLOL

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Nineteen patients (pts) with severe angina pectoris entered a double blind controlled study to evaluate the effect of oral propranolol (P) on exercise tolerance measured with a bicycle ergometer, and left ventricular (LV) function measured by echocardiography and systolic time intervals. In the P treated group dosage was increased from 80 to 320mg/day. Studies , which included blood P levels, were obtained before treatment and at each P dose. On P 80mg/day total work increased by 128% from 765±125 to 1,785±285 kpm when compared to pre-treatment performance ($p < .01$). At dose levels of P $\geq$ 160mg total work performance decreased, but remained higher than at control levels. In the P treated group LV function decreased progressively with increasing drug dose. As measured from the echocardiogram, maximum endocardial posterior wall velocity fell 35% from 62±19 to 40±11 mm/sec, ejection fraction fell by 12% from .68±.05 to .60±.04, and end diastolic volume increased from 90±23 to 111±28 ml/m^2, (all $p < .05$). PEP/LVET significantly increased with each dose increment and correlated with the decrease in ejection fraction measured from the echocardiogram, ($r = .75$, $p < .01$). There was no correlation between blood level of P and improved work performance. Thus exercise tolerance was maximally improved with dosages of 80mg/daily. At higher dose levels LV function deteriorated and exercise work fell. Non-invasive assessment of LV function proved more valuable than drug levels in management of patients with angina pectoris and provides a guide to optimal adjustment of dosage.

ANODAL INFLUENCE ON VENTRICULAR FIBRILLATION

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The difference between cathodal, anodal and bipolar fibrillation threshold was investigated in open chest anesthetized dogs with SA nodal destruction and ventricular pacing at 150/min. Constant current 2 msec duration rectangular cathodal, anodal or bipolar pulse trains of 100 Hz were applied via the pacing electrode(s) for 500 msec to the left ventricular apex with the onset of the R wave during interruption of ventricular pacing. The current required to fibrillate using cathodal trains was 2.5 times larger than that required for anodal or bipolar trains, both of which had equal fibrillation thresholds. Electrograms indicated shorter refractory periods with more rapid ventricular responses for anodal or bipolar trains than for cathodal. Fibrillation threshold was also determined after two consecutive premature ventricular contractions by a 2 msec pulse. Starting from total refractory, a time range of vulnerability was determined in which anodal fibrillation threshold was less than cathodal. It is hypothesized that lower anodal or bipolar fibrillation threshold is due to their shorter refractory period and lower threshold in relative refractory. These data support the observed greater relative frequency of ventricular fibrillation in the presence of bipolar cardiac stimulation than unipolar, and suggest that unipolar cathodal stimulation is intrisically safer than bipolar, especially when fibrillation threshold is reduced as with myocardial ischemia.

ANGIOGRAPHIC PATTERNS EARLY IN THE ONSET OF THE CORONARY SYNDROMES

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Little information is available regarding angiographic patterns soon after the onset of different coronary syndromes. Coronary angiography was performed in 300 patients (pts) within one year of onset of symptoms of coronary artery disease. 164 pts had angina pectoris alone (AP), 63 subendocardial myocardial infarction (SMI), and 73 transmural myocardial infarction (TMI). In the three groups there was an equal distribution of one, two, or three vessel disease (50% or more obstruction). The distribution of obstruction was also similar in the three groups--left anterior descending 81%, right coronary 60%, circumflex 49%, left main coronary 7%. Of the vessels not totally occluded, the degree of stenosis was also similar in the three groups. However, the percentage of vessels with total occlusion was much higher in TMI (53%) than in the SMI (30%) or AP (24%) groups. Of the total number of diseased vessels with associated collaterals (30%), 84% were completely occluded and only 16% were not. The association of collaterals with occlusion was greater in AP (85%) and SMI (85%) than in TMI (61%) pts. The presence of collaterals was not apparently related to duration of symptoms. Ventriculography was performed in 297 pts. Localized or diffuse reduction of contractility was present in 75% of TMI and only in 29% of SMI and 26% of AP pts. The degree and distribution of coronary lesions could not be correlated with hypertension, cigarette smoking or elevated serum lipids in any of the three groups.

In conclusion, within one year of onset of AP, SMI or TMI, angiography showed strikingly similar patterns in all three groups, apart from the high incidence of vessel occlusion and abnormal ventriculography in TMI. Coronary angiographic patterns were unrelated to risk factors in this selective group of patients.

CORONARY PATHOLOGY AND LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY HEART DISEASE

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Detailed clinical and laboratory observations have shown that a great disparity may exist between the severity of coronary lesions and heart muscle damage in patients with coronary heart disease (CHD), a disparity which depends on the heart's ability to protect jeopardized muscle through collateral circulation. In 300 CHD patients undergoing coronary arteriography, coronary morphology was correlated with ventriculographically-observed left ventricular contractions and left ventricular dynamics measured by post-contrast injection end-diastolic pressure (EDP) and ejection fraction (EF). Single-vessel involvement did not significantly alter ventricular dynamics, except in lesions proximal to the origin of the first septal artery (SA); here the EDP was increased to 21± 7 mm Hg. The incidence of left ventricular asynergy and proximal lesion aneurysm was markedly higher (43%) than in lesions involving other vessels. Patients with triple-vessel disease showed decreased left ventricular function: lesions proximal to the first SA - EF 44± 13.2%, EDP 28± 8.2 mm Hg and lesions distal to the first SA - EF 48± 14.3%, EDP 22± 7.3 mm Hg. In this patient group, the occurrence of left ventricular aneurysms was identical to that in lesions proximal and distal to the first SA (39%).

These findings clearly confirm the very important role that collateral blood flow through the septum, via either the first SA or the posterior descending system, plays in preserving myocardium.

CLINICAL USE OF AN ISOTOPIC CARDIAC PACEMAKER.

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Long-lived radioisotope pacemakers were first used by Laurens and Piwnica in April of 1970. The Medtronic-Alcatel pacemaker is of the demand type. The fuel capsule contains about 150 mg of Plutonium-238. Heat is converted into electricity by a bismuth telluride thermocouple. Radiation level at the surface is 3 mrem/hr and is expected to reach 5 mrem/hour after 5 years, well within safety limits. The design life of the pacemaker is 10 years. It has been extensively tested and found to be safe under all conditions of credible accident.

The first clinical use in the United States was made by us in July of 1972 and since then we have treated 18 patients. Primary installations (5) were made with myocardial electrodes to avoid potential dislodgement, occasionally seen with endocardiac electrodes. Replacements (13) were made with myocardial or endocardiac electrodes which had been shown to be stable.

All patients have made an uneventful recovery and all pacemakers have functioned satisfactorily. At the present time, about 400 such units have been used, mostly in Europe, and at the time of this writing, pacemaker malfunction has not been observed.

EFFECT OF RESTORATION OF NORMAL LEVELS OF MEMBRANE POTENTIAL ON OUABAIN TOXICITY IN CARDIAC PURKINJE FIBERS.

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A principal manifestation of ouabain (O) toxicity in Purkinje fibers (PF) is transmembrane depolarization presumably due to inhibition of the Na-K pump. To determine whether other manifestations of O toxicity derive from this principal effect, we restored the transmembrane potential (TMP) to control levels during O exposure and studied the effect of this maneuver on action potential (AP) parameters. A two-microelectrode technique was used. One electrode passed current while the other measured TMP. A third electrode was used for extracellular stimulation (cycle lengths 630-1300 msec). Shortened sheep cardiac PF (previously described) were superfused in vitro with Tyrode sol. (K=4.0mM; T,36°C). During O ($2x10^{-7}$M) superfusion, polarizing current was passed intermittently to restore the TMP to control levels. The rate of rise and overshoot of the AP returned towards control levels. Spontaneous activity that had developed during O toxicity was suppressed. O-induced enhanced phase 4 depolarization (P4D) was decreased. In PF that had become inexcitable, restoration of the TMP to control levels restored excitability. Repetitive stimulation at this time resulted in a gradual increase in P4D, escape from the stimulus, and depolarization of the fiber. These results indicate that restoring TMP to control levels can substantially ameliorate the toxic effects of O on the AP. In conjunction with voltage clamp experiments (previously described) these results further support the hypothesis that O exerts its effects on PF by disrupting the integrity of the Na-K pump.

PRELOAD DEPENDENCE OF EJECTION FRACTION

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The effects of varying preload on left ventricular (LV) contraction were examined by means of beat-to-beat measurements of LV volume, derived from biplane cineangiograms, over a sequence of 5-8 cardiac cycles in six patients with atrial fibrillation. The level of myocardial inotropic state was determined simultaneously from the rate of isometric LV pressure rise, recorded by means of a catheter-tip micromanometer, at a common developed (dev) isometric pressure (P) of 40 mmHg (dp/dt/Pdev 40). Variations in LV end-diastolic volume (EDV), ejection fraction (EF), and dp/dt/Pdev 40 were expressed as percent changes over values observed at the smallest level of EDV in each patient. Substantial variations in preload, or EDV, (avg. +22.7 ± 2.9%) were accompanied by comparable and directionally similar changes in EF (avg. +18.1 ± 3.9%). However, dp/dt/Pdev 40 exhibited no variation with increments in preload (avg. change +1.3 ± 2.6%), indicating that changes in myocardial inotropic state were not responsible for beat-to-beat changes in EF. When measurements of EF were "corrected" i.e. normalized by dividing by EDV (NEF), preload-induced variations in EF were no longer evident (avg. change -2.7 ± 1.9%). Thus, because EF varies substantially with changes in preload alone, the value of this commonly-employed parameter as a comparative indicator of LV performance is limited. Normalization of EF (NEF) for corresponding EDV may provide a more accurate estimate of LV myocardial function.

BENEFICIAL EFFECTS OF PROSTAGLANDIN F2α IN EXPERIMENTAL MYOCARDIAL INFARCTION.

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The ability of prostaglandin F2α (PGF2α) infusion to modify the hemodynamic and biochemical alterations resulting from myocardial infarction (MI) was investigated. PGF2α (30µg/kg,i.v.) or saline was infused in cats subjected to ligation of the left anterior descending coronary. Post-infarction survival times of PGF2α-treated cats was 353% ($p<0.01$) greater than saline treated animals. Plasma activity of myocardial depressant factor (MDF), a peptide involved in the development of lethal shock, was 347% higher in saline treated infarcted cats than in cats receiving PGF2α. Cardiac output (CO) of saline treated infarcted cats fell to 53% of control at 60 min. and to 38%, 180 min. postinfarction. Whereas, CO of PGF2α treated cats fell to 69% of control at 60 min. and only to 62%, 180 min. postinfarction. Following infarction the increases in total peripheral resistance, plasma lysosomal enzyme activity, plasma MDF activity, and splanchnic lysosome fragility seen in saline treated cats was significantly attenuated by PGF2α infusion. The protective action of PGF2α appears to be related to its ability to maintain lysosome integrity of ischemic tissues and subsequently, prevent the formation of the cardiotoxic peptide-MDF.

DERANGEMENTS OF MYOCARDIAL METABOLISM DURING ISCHEMIC ARRHYTHMIAS.

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Metabolic effects of arrhythmias in ischemic and non-ischemic myocardium were determined in 17 dogs. Following LAD intracoronary balloon occlusion, myocardial oxygen extraction [O_2(A-V)], lactate (LB) and potassium (KB) balances were measured separately from both occluded (O) and nonoccluded (NO) perfusion zones of the myocardium. Results were compared during preocclusion control (POC), after occlusion but before arrhythmias (Pre-A), when ischemic ventricular arrhythmias supervened (A), and during ventricular fibrillation (VF) (*$p < 0.05$ relative to POC):

		POC	Pre-A	A	VF
O_2 (A-V) (%)	NO	58.0	64.1 *	61.8 *	39.6 *
	O	55.7	62.8 *	62.5 *	42.7 *
LB (A-V)/A (%)	NO	31.1	23.3	18.1 *	-26.8 *
	O	33.3	14.9 *	3.7 *	-66.9 *
KB (A-V) (mEq/L)	NO	0.01	- 0.06	- 0.16*	- 0.25*
	O	0.01	- 0.21*	- 0.33*	- 0.45*

Following occlusion (Pre-A), oxygen extraction increased in both O and NO; significant K^+ loss and abnormal lactate metabolism occurred in the occluded segment.

When arrhythmias supervened, further deterioration of abnormal lactate metabolism and increased K^+ loss occurred in NO as well as in O segments, demonstrating onset of "global" myocardial metabolic dysfunction. VF exhibited severe lactate production and increased K^+ loss in both NO and O zones. Oxygen extraction dropped drastically in both zones during VF.

Arrhythmias and VF after coronary occlusion cause significant metabolic derangements in both NO and O regions.

EFFECT OF SURVEILLANCE ON PACER LONGEVITY AND PATIENT RISK

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Evaluation of pacemaker follow-up is necessary to ensure maximal pacer longevity and minimal patient risk at reasonable cost to the health economy. To assess our program, we reviewed 633 pulse-generator replacements performed over the past 5 2/3 years. The mean duration of all units, removed for all reasons, was 20.7 mos; 169 elective replacements (26.9%) averaged 24.9 mos; and 310 units replaced for failure (50.3%) averaged 21.6 mos. (90.1% manufacturers' corroboration in 128/142 units). In the period prior to establishing a Pacemaker Clinic, mean pacer life was 22 mos; with a follow-up Clinic using an elective replacement schedule, mean pacer life was 21 mos. In the latest period, with a computer-based Pacemaker Centre, co-operating network of peripheral clinics and trans-telephone evaluation, pacer life averaged 23 mos; however 24 units, monitored only by telephone, lasted 26.6 mos. Of 104 patients currently followed by telephone analysis, mean duration of functioning implants is 30.5 mos for asynchronous (range 18.0-44.5 mos) and 24.7 mos for demand units (range 18.0-40.0 mos). Emergency replacements fell from 55% (1968) to 10% (1973); return of symptoms occurred in 66% initially and 27% recently. A Pacemaker Clinic alone may not increase pacer longevity but does reduce risk and morbidity. Telephone surveillance permits extended longevity but with considerable time, personnel and cost implications, and possibly patient anxiety. The average duration of implants in the present sample of patients on telephone evaluation approximates the industry recommendation for removal. Is an elective replacement schedule a reasonable, effective and less expensive alternative?

CORONARY COLLATERAL FUNCTION IN PATIENTS WITHOUT OCCLUSIVE CORONARY ARTERY DISEASE.

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Little is known of the functional capacity of coronary collaterals in humans without occlusive coronary artery (CA) disease. We therefore measured peripheral coronary pressure (PCP) and retrograde flow (RF) from CA at aortic valve replacement in 7 patients without occlusive CA disease. Using a t-connection interposed in left (L) and right (R) coronary perfusion lines, data were obtained during brief proximal occlusion of each line. PCP was expressed as a fraction of perfusion pressure (PP) and collateral resistance (CR) was calculated as PP/RF. Mean values were as follows:

Occluded perfuser	RF (ml/min)	CR (mm/Hg/ml/min)	PCP (mm Hg)	PCP/PP
LCA	1.8	46	13	0.19
RCA	1.2	62	16	0.24

In contrast, previous studies of well-collateralized distal segments of diseased CA revealed mean RF 15.7, CR 5.1, and PCP/PP 0.50. Under the conditions of study, all vessels interconnecting the non-diseased RCA and LCA delivered flow and pressure less readily than collaterals to a single distal segment of a diseased CA. Thus, collaterals in patients without diseased CA have an extremely limited capacity to transmit either flow or pressure. The absolute values of RF were small relative to the muscle mass perfused by each CA, suggesting that perfusion of only one CA in man during operation may not provide substantial perfusion for large portions of myocardium. Comparison of performance of collaterals supplying diseased and non-diseased CA indicates that proximal occlusion may be an important factor stimulating enhancement of collateral function.

DUAL ISOTOPE MYOCARDIAL IMAGING: ASSESSMENT OF CORONARY FLOW RESERVE FROM CHANGES IN REGIONAL PERFUSION DURING CORONARY HYPEREMIA IN ANIMALS AND MAN

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Resting coronary flow and regional distribution are normal despite up to 85% diameter coronary stenosis. Accordingly, regional perfusion was evaluated during hyperemia in order to quantify maldistribution occurring at high flow rates but not at rest. In 8 open chest dogs quantitative regional distribution of left coronary flow was determined by electromagnetic flowmeters on the anterior descending and circumflex arteries and simultaneously by double radionuclide studies. Coronary flow was varied from basal to maximum by intracoronary injections of Hypaque-M, 75%, previously shown to be a potent, repeatable stimulus for maximal hyperemia. Malperfusion due to coronary stenoses quantified with the gamma camera correlated closely with results by electromagnetic flowmeters (r=0.96). In the presence of balanced lesions on the circumflex and anterior descending arteries, hyperemic responses were reduced and regional perfusion was normal. To demonstrate the applicability of this approach in man, 12 patients were studied by intracoronary injection of ^{113m}Indium macroaggregated albumin (MAA) in the resting state and ^{99m}Tc MAA during the hyperemia following the injection of intracoronary contrast media. Scintiphotographs from patients with moderate to severe angiographic coronary lesions demonstrated normal regional distribution at rest but maldistribution during hyperemia. The results in patients also demonstrated that collaterals failed to maintain normal distribution during hyperemia despite normal perfusion at rest.

TRICUSPID LEAFLET PROLAPSE AS A COMPONENT OF THE SYSTOLIC MURMUR-CLICK SYNDROME

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Patients with systolic murmur and/or clicks are often proven to have prolapse of the mitral leaflets. In order to assess the tricuspid valve in such cases, right ventriculography was performed in 61 patients. There were 51 females and 10 males. Systolic murmurs were present in 47 cases and 32 had clicks. Thirty-seven had nonanginal chest pains and 23 complained of palpitations. Left ventriculography revealed definite prolapse of the mitral valve in 52 cases and ventricular asynergy was seen in 43. Right ventriculography was performed in the right anterior oblique projection. Late systolic prolapse of the tricuspid valve was seen in 32 patients (52.4%); including all leaflets in 15 cases and limited to the inferior leaflet in 17. Deformities of the right ventricular musculature, tricuspid ring and/or leaflets were seen in an additional thirteen cases. In 17 cases (27.9%) the degree of tricuspid prolapse was greater than that of the mitral leaflets. This study demonstrates that the systolic murmur-click syndrome may be associated with prolapse of either or both of the atrio-ventricular valves.

ELECTROPHYSIOLOGIC ALTERATIONS IN CARDIAC DYSRHYTHMIAS: ANTIARRHYTHMIC EFFECTS OF APRINDINE.

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Studies on isolated cardiac tissue superfused with low concentrations of Aprindine [N-phenyl-N(3-diethylamino propyl)-2-indanylamine HCl] were initiated in order to determine the effects of this agent upon normal tissue and in tissues made dysrhythmic under conditions simulating infarction. Membrane potential, rate of rise of phase 0, action potential amplitude, duration, and impulse conduction were assessed utilizing intracellular electrodes. In normal non-automatic Purkinje fibers, Aprindine depressed the rate of rise of phase 0 with a concomitant reduction in action potential amplitude, duration and at times in membrane potential. With prolonged superfusion, conduction became altered with varying degrees of block, and exhibited the clinical counterpart of the Wenkebach structure. In Purkinje fibers rendered automatic by stretch, hypoxia, digitalis or catecholamines, the slope of phase 4 depolarization was reduced and eventually abolished with Aprindine. The onset of automaticity, by the above interventions, was prevented by prior administration of Aprindine. Conduction depression, (and block at high doses), also occurred in muscle with this agent, but was less sensitive than Purkinje tissue. The alteration in conduction in association with abolition of automaticity, could thus abolish a tachycardia. The effects occurred with low doses and persisted for a long time. This, with the reported long biological half-life, would minimize the requirement for repeated administration for the prevention and treatment of cardiac dysrhythmias.

MORPHOLOGY OF THE CORONARY ARTERY-BYPASS GRAFT ANASTOMOSIS

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Sixty bypass graft anastomoses in 34 patients dying in the immediate operative period (25 patients) or up to 5 months (9 patients) after direct coronary revascularization were studied at autopsy by angiography and serial histologic sectioning of the graft to artery anastomosis. Graft patency was 90% (54/60). Most patent grafts including their proximal connection showed no significant narrowing. Comparison of the preoperative and postmortem angiograms and histology showed that 23 anastomoses and the corresponding coronary artery were widely patent, 16 coronary arteries had a significant (> 70%) new narrowing and 21 arteries had a new total occlusion. New coronary occlusions and narrowings occurred adjacent to either the proximal or distal ends of the anastomosis and were due to compression or loss of circumference of the arterial lumen (68%), thrombus formation (16%) or mural dissection of the coronary wall (16%) and appear related to suture placement or surgical endarterectomy. A local atheroma and/or small coronary lumen were significant factors predisposing to these occlusive changes. Fewer changes were identified in those instances where the distal end of the arteriotomy terminates at the apex of a branch point rather than continuing down one of the two branches.

The findings emphasize the importance of careful artery selection for bypass, the need to avoid local vascular disease and the difficulties encountered in the presence of local atheromata or a small coronary lumen.

RELATIVE EFFECTS OF LEFT VENTRICULAR MASS AND WALL THICKNESS ON DIASTOLIC STIFFNESS

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The influence of left ventricular (LV) mass and posterior wall thickness at end diastole (h_p) on LV diastolic stiffness has been examined in 24 patients with various forms of heart disease by use of a combined ultrasonic and hemodynamic technique. The slope of late diastolic LV pressure-diameter relations ($\Delta P/\Delta D$) was calculated and used as a measure of effective diastolic stiffness (S) late in diastole. S was normalized for average LV pressure during the interval of measurement ($\bar{P}$) as $S/\bar{P}$, called S_N. Ultrasonically determined LV mass index (LVMI) and h_p were measured in each patient simultaneous with the determination of S and S_N.

The range of h_p was 5.6 to 18.6 mm; it was highest in aortic stenosis, and lowest in mitral stenosis. Linear regression of h_p against S and S_N showed significant correlation with r=.85 and .75, respectively ($p < .001$ for each). LVMI ranged from 42 to 387 gm/M^2 and 11 of the 24 patients had increased LVMI (>124 gm/M^2). In this group of 11 patients, h_p varied widely (increased in 6, normal in 5), depending on the nature of the underlying disorder (increased h_p in amyloidosis and concentric hypertrophy, normal h_p in dilated, failing LV). Within this group of 11 patients, h_p was an excellent predictor of S (r=.86, $p < .001$) while LVMI itself was a poor predictor (r=.50, NS), suggesting that increased LV mass is a determinant of diastolic stiffness only in so far as it is associated with increased h_p.

In conclusion, these observations indicate that h_p is a major determinant of LV diastolic stiffness, independent of total LV mass.

TOTAL BODY ANGIOGRAPHY IN PATIENTS WITH DIFFUSE ATHEROSCLEROSIS

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It is a well known fact that atherosclerosis affects frequently more than one area of the cardiovascular system. Using the brachial approach, with local anesthesia, and in one session we were able to study angiographically the coronary arteries, supra aortic vessels, abdominal branches of the aorta and/or the peripheral circulation, which were registered in a 35 mm. film with a 9 inch image intensifier and overframing. Out of a total of 180 cases, we evaluated the first 100 patients in whom multiple angiographic studies were performed. The primary cause of the angiography was A.S.H.D. in 47 patients and A.S.O. (atherosclerosis obliterans) in 44 patients which constitutes 91% of the cases. As a secondary study we did 20 coronary arteriographies, 55 selective renal arteriographies, 31 carotid vertebral opacifications and 17 peripheral arteries visualizations. Five aortic aneurysms were diagnosed. In this report we discuss the technic, indications and findings of these multiple studies.

CARDIOMYOPATHIC FEATURES IN THE SYNDROME OF SYSTOLIC CLICK, MURMUR AND MITRAL VALVE PROLAPSE.

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Twenty-six patients with systolic clicks, murmurs, and prolapsed mitral valve leaflets were studied because of distressing anginal symptoms or troublesome arrhythmias. Cardiac catheterization revealed normal coronary arteries and a high incidence of left ventricular (LV) dysfunction. The patients, 20 of whom were women, averaged 41 years of age. Thirteen of the 22 patients with angina experienced pain of sufficient severity to warrant hospital admission for suspected acute myocardial infarction. Twenty of 26 had abnormal ECG's which included sinus bradycardia, 1^o, 2^o and 3^o block, atrial and ventricular arrhythmias and abnormal ST-T wave vectors. Three had patterns of healed transmural infarctions and 5 of 16 had positive exercise tests. LV dysfunction was hemodynamically documented in 20 patients by either elevated LV end diastolic pressure, low resting cardiac index, or inappropriate rise in cardiac index during exercise. In the remaining 6, impaired LV dynamics were demonstrated angiographically. Left ventriculography revealed mitral valve prolapse in all patients, mitral regurgitation in 20, and mild to moderate LV hypertrophy in 14 patients. Contractility, as judged angiographically, was significantly impaired in 13 patients. They had marked hypokinesis of the anterolateral wall of the LV resulting in the appearance of an unusual prominent convexity in this portion of the ventricle in end systole and early diastole. Seven others had similar impairment of LV contractility, but less severe. These results indicate that the syndrome of prolapsed mitral valve leaflet has a significant component of LV dysfunction which has not been previously emphasized.

ULTRASOUND EVALUATION OF SYSTOLIC ANTERIOR SEPTAL MOTION IN PATIENTS WITH AND WITHOUT RIGHT VENTRICULAR VOLUME OVERLOAD

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Systolic anterior septal motion (SASM) has been proposed as a reliable indicator of right ventricular volume overload (RVVO). Accordingly, we studied 244 patients (pts) without clinical or catheterization evidence of RVVO employing the ultrasound continuous recording technique. At the level of the mitral valve SASM was present in 111 pts; in 39 pts the septum did not move during systole while in 74 pts, septal motion was variably anterior and posterior during the same recording. However, at the level of the chordae tendinae, 225 of the 244 pts (92%) had normal posterior septal motion. The other 19 pts had severely impaired left ventricular function. In 30 pts with RVVO, 16 had abnormal septal motion at the level of the chordae tendinae (13 with SASM and 3 with no movement). To evaluate septal motion further, 100 normal subjects were studied using a phased multicrystal ultrasound system (by Bom) which provides a saggital plane image of the cardiac structures. In all 100 subjects the superior septum moved anteriorly in systole with the aortic root, whereas the midportion of the septum acted as a "hinge" for the inferior portion, which moved posteriorly. In 8 of 20 pts with RVVO, the entire septum moved anteriorly during systole; variable patterns occurred in 5 pts, while normal septal motion was present in 7 pts. We conclude: 1) that SASM is usually present when septal motion is recorded at the mitral valve level in pts with and without RVVO, and 2) that abnormal septal motion is not a constant echocardiographic finding in pts with RVVO even when recordings are performed at the level of the chordae tendinae.

DIAGNOSIS VALUE OF THE ELECTROCARDIOGRAM IN RECURRENT MYOCARDIAL INFARCTION : AN AUTOPSY STUDY.

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Of 294 consecutive autopsies data of patients (pts) dying of myocardial infarction (MI), 45 with recurrent MI, were selected and correlated to the electrocardiogram (ECG). ECGs were first interpreted without knowledge of pathological findings. Accuracy of the ECG diagnosis was then evaluated. Results were classified into 3 categories : (1) in 14 pts (31,1%) diagnosis was correct as both old and recent MIs were recognized; (2) in 26 pts (57,7%) diagnosis was incomplete due to the lack of ECG signs of either the old (8 pts) or recent (18 pts) MI; (3) in 5 pts (11,2%) MI could not be detected on the ECG. Many factors contribute to obscure the diagnosis : lack of serial tracings especially when ECG have become normal after the previous MI; presence of intraventricular conduction disturbances, left bundle branch block mainly; recurrent MI occurring in the subendocardial region or in an already infarcted area (31 of 45 pts); atypical ECG patterns, the absence of early ST-T changes being quite remarkable.

It is concluded that, ECG is inaccurate in recognizing recurrent MI as correct diagnosis was possible in only 14 of 45 pts (31,1%), the recent MI being twice more often unrecognized than the old one.

ANTI-ARRHYTHMIC EFFICACY OF APRINDINE IN ACUTE MYOCARDIAL INFARCTION.

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Aprindine (A) is a new, long-acting, orally effective anti-arrhythmic drug, with electrophysiologic properties akin to those of Lidocaine (L). In 40 consecutive patients (pts) admitted to the CCU with a diagnosis of acute myocardial infarction (MI) and evidence for ventricular irritability, a double-blind randomized study was undertaken comparing the effectiveness of oral A (200 mg, then 100 mg q 12 h for 60 h) and intravenous L (2 mg/min for 60 h) in preventing ventricular arrhythmias. These were detected by on-line computer monitoring of the ECG, standard monitoring, recording of a 60 sec rhythm strip every two hours, and observation by nurses and doctors. 5 pts (1A, 4L) proved not to have MI. Treatment was considered excellent if no ventricular arrhythmias were observed; good if no serious arrhythmia occurred; a failure if VF, VT, doublets, or early VPB's appeared despite therapy :

	Excellent	Good	Failure
A	13	2	4
L	5	2	9

Gas chromatographic analysis of serum levels of A gave the following values (mg/l) : 0.6-1.1 12 h after first dose; 1.7-2.8 60 h after first dose; 0.9-2.0 48 h after last dose. The only possible symptoms of drug toxicity involved the central venous system : nightmares, hallucinations, restlessness. 2 A pts and 3 L pts were so affected.

1 A pt and 2 L pts died during the first 7 days after admission. Oral Aprindine compares favourably with intravenous Lidocaine in preventing ventricular arrhythmias after acute MI.

DETERMINANTS OF REVERSIBILITY OF LEFT VENTRICULAR FUNCTION AFTER AORTOCORONARY BYPASS SURGERY

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Left ventricular (LV) hemodynamics and contractile patterns were evaluated in 104 patients (pts) before and after aortocoronary bypass surgery. All pts had patent grafts (171). Group I consisted of 44 pts with single grafts. Mean LV end-diastolic pressure (LVedp), volume and ejection fraction (EF) did not change. Twenty-four pts who had asynergy preop revealed 16 with a normal contractile pattern postop. Group II consisted of 47 pts with double vein grafts. Significant decrease in LVedp ($p < 0.005$) and increase in EF ($p < 0.001$) postop. Asynergy in 29 pts preop revealed postop 15 synergy, 3 improved, 9 no change and 2 became worse. Group III consisted of 10 pts with triple vein grafts. EF significantly increased postop ($p < 0.01$). All but 2 of the 8 pts with asynergy preop showed synergy postop. Synergy in 43 pts preop, with one exception, persisted postop. Asyneresis in 41 instances preop revealed postop 38 (93%) had normal wall movement. In 29 instances of preop akinesia of a wall, only 8 (28%) showed a return to normal wall movement. Unstable angina pectoris alone did not influence reversibility of abnormal contractile patterns. Unstable angina pectoris with absence of abnormal Q waves in the EKG was noted in 23 pts with asynergy. All but 1 pt had synergy postop. Pts with infarction pattern on the EKG, when accompanied by asynergy, were unlikely to have a normal contractile pattern postop (4/23). Reversibility of LV function after surgery is common, not related to number of grafts, but is related to type of LV wall abnormality, EKG and clinical state of pt.

THE EJECTION FRACTION AS A PREDICTOR OF SURVIVAL IN PATIENTS WITH CARDIOVASCULAR DISEASE

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To ascertain the predictive value of the left ventricular ejection fraction (EF) regarding survival, the records were reviewed and follow-up obtained on all patients undergoing cardiac catheterization and who had adequate left ventricular volume measurement by quantitative angiography at the VA Hospital from 1960 to 1970. Actuarial survival curves were constructed for 193 adult patients (age range 20 to 73, mean age 48) and with cardiovascular diagnosis predominantly valvular (59%) and coronary (15%) heart disease. The survival curves for those with borderline EF (45-54%) was the same as that for the group with normal EF ($\geq$ 55%) for the first six years following catheterization (5-year survival 58-60%, 50% dead 6.0-6.8 years), but at ten years the group with normal EF had a 38% survival while the group with borderline EF had a 25% survival. Those with moderate depression of EF (30-44%) had a 5-year survival of 37%, and 50% were dead by 2.8 years. Those with severe depression of EF ($\leq$ 29%) had 5-year survival of 28% with 50% dead by 1.8 years. The 59 cardiac surgical patients with EF $\geq$ 50% had better survival (5-year = 60%, 50% dead at 9 years) than the 51 medical patients with EF $\geq$ 50% (5-year = 43%, 50% dead at 4.2 years). The 31 surgical patients with EF $\leq$ 49% had 5-year survival of 52% with 50% dead at 5.4 years, while the 54 medical patients with EF $\leq$ 49% had 5-year survival of 24% with 50% dead at 1.4 years. EF is an important determinant of survival following catheterization with minimal reduction in EF being associated with decreased late survival. More severe impairment of EF is associated with shorter survival in both medical and surgical groups. Medical patients had shorter survival than surgical patients with comparable EF.

THE DIFFERENTIAL DIAGNOSIS OF ANOMALIES OF THE GREAT VESSELS BY REAL-TIME, TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Walter L. Henry, MD; Barry J. Maron, MD; James M. Griffith; and Stephen E. Epstein, MD, NHLI, Bethesda, Md.

The recent development of a sector-scanner that produces real-time, two-dimensional echocardiograms has made possible cross-sectional imaging of the heart. In this scanner system, a transducer is angled rapidly through a 30 or 45 degree sector and generates 30 high resolution images per second, each one containing 100 individual ultrasound data lines. To determine if this system is useful in the differential diagnosis of congenital anomalies of the great vessels, we studied 23 pts (age 2 to 33 yrs) with cyanotic congenital heart disease previously diagnosed by cardiac catheterization. Images were generated perpendicular to the long axis of the heart at the level of the origin of the great vessels. Satisfactory great vessel visualization was obtained in 20 of 23 pts. Vessels in cross-section appeared as circles; those sectioned longitudinally appeared sausage-shaped. Three patterns were seen: A) a large single circle, seen in 2 pts with truncus arteriosus and 3 with pulmonary atresia; B) 2 adjacent circles, seen in 11 pts with transposition of great vessels including one pt with Taussig-Bing and 2 with double outlet right ventricle; and C) a circle with an anterior sausage-shaped structure curving laterally and inferiorly from right to left, seen in 4 pts with tetralogy of Fallot. This latter pattern, also seen in 11 normal subjects and 20 pts with acquired heart disease, is characteristic of normally related great vessels. In addition to anatomic relationships, absolute measurements of vessel diameter were made. We conclude that two-dimensional echocardiography is a quick, non-invasive and extremely powerful technique for diagnosing congenital anomalies of the great vessels.

CHANGES IN THE SUBUNIT COMPOSITION OF MYOSIN FROM HEARTS UNDERGOING HYPERTROPHY

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Experimentally induced changes in the contractility of skeletal muscle appear to be associated with structural and enzymic alterations in myosin. To determine whether the altered contractility of hypertrophied myocardium is associated with analogous changes in myosin from heart muscle we produced right ventricular hypertrophy in 20 rabbits by constriction of the pulmonary artery for one week, evaluated papillary muscle mechanics, analyzed the subunit composition of purified myosin from the same hearts by SDS gel electrophoresis, and assayed myosin ATPase activity. As anticipated from previous reports, the force-velocity relation was significantly depressed in papillary muscles from hypertrophied hearts ($n = 8$) compared to those from normal hearts ($n = 8$) matched for cross sectional area. Myosin from sham operated animals exhibited only two low molecular weight (MW) components (MW = 20,000 and 27,000, $n = 5$ preparations). In contrast, myosin from hypertrophied hearts exhibited a third low molecular weight component (MW = 16,000) and exhibited an electrophoretic pattern similar to that shown by white skeletal muscle. EDTA-activated ATPase activity was significantly depressed in myosin from hypertrophied hearts ($n = 5$) compared to controls ($n = 5$) averaging 240 ± 10 and 281 ± 8 nmoles/mg protein/min respectively ($p < .05$). These results indicate that myosin from myocardium undergoing hypertrophy exhibits alterations which may be related to changes in contractility in the intact muscle.

IDIOPATHIC PAROXYSMAL VENTRICULAR TACHYCARDIA IN CHILDHOOD

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This is a report on 6 children 3-10 years of age with idiopathic paroxysmal ventricular tachycardia (IPVT) who have been observed in the last two years. The evaluation included clinical, electrocardiographic (ECG), and roentenographic examinations, exercise tolerance with ECG monitoring, 24 hour urinary vanilmandelic acid and catecholamine excretion, serum T_4, electrolytes, blood gases, and electroencephalogram. Therapeutic evaluation included acute response to lidocaine (LI) and procainamide (PA) and chronic therapy with PA and/or propranolol. Holter monitoring for 24 hour periods before and after changes in therapy was used to evaluate the frequency, duration, and time of occurrence of attacks. No cause of IPVT was found in five patients; one patient had clinical evidence of tuberous sclerosis and angiographic evidence suggestive of an intracardiac tumor. LI was the most effective drug for treating two of the patients with acute syncopal and hypotensive attacks. PA was reliable in preventing attacks, and serum PA levels of 7-15 µg/ml were necessary to abolish or decrease the frequency of the arrhythmia as shown in 24 hour ECG recordings. In two patients the firm diagnosis of IPVT could only be made by analysis of the Holter recordings. These cases emphasize that (1) the initial presentation and frequency of attacks varies greatly among patients, (2) LI is most effective for acute symptomatic attacks, (3) relatively high serum levels of PA are necessary to control the arrhythmia on a prophylactic basis, (4) Holter monitoring was found invaluable in establishing the initial diagnosis and assessment of therapeutic results.

SICK SINUS SYNDROME IN CHRONIC CHAGAS' HEART DISEASE.
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Sick Sinus Syndrome (SSS) had not been reported as such in Chronic Chagas' Heart Disease (CCHD). The following study was conducted to evaluate the incidence and clinical picture of SSS in CCHD. The clinical records of 300 pts. with CCHD were reviewed. The mean age, the absence of angina and the other clinical features did not suggest coronary artery disease. The ECG of 15 pts. were consistent with SSS and divided into two groups. Group I (5 pts.) did not reveal associated A-V conduction disturbances; the mean age was 38.6 yrs. and there was no evidence of congestive heart failure (CHF). Group II included 10 pts. in whom SSS was associated to A-V conduction disturbances; the mean age was 45.9 yrs. CHF was present in 30 %. Dizziness and Stokes Adams Syndrome (SAS) were observed in both groups: 40% in group I and 20% in group II. Permanent pacemakers could be implanted in only 33% of pts. The analysis revealed that SSS is not a common isolated finding in CCHD. However, this disorder was associated with severe symptoms, including SAS. The ECG abnormalities associated to SSS further indicate severe damage to atrial, junctional and ventricular tissue (P wave abnormalities, intermittent slow junctional and ventricular rhythms, A-V block, BBB, hemiblocks, PACs, PVCs, etc.) with involvement of pacemakers and conducting system. Relatively long periods of atrial and ventricular asystole were recorded by Dynamic ECG, indicating severe depression of sinus node and subsidiary pacemakers.

PRODROMA OF VENTRICULAR FIBRILLATION IN ACUTE ISCHEMIA: EFFECT OF HEART RATE AND ANTI-ARRHYTHMIC DRUGS
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The efficacy of antiarrhythmic drugs in the prehospitalization phase of acute myocardial infarction has not been established. In 25 open chest dogs with the anterior descending coronary artery (ADCA) temporarily occluded (2-6 min), ischemic zone subepicardial electrograms (IZE) were recorded. Ventricular arrhythmias (including premature contractions, tachycardia and fibrillation) occurred in all and followed increasing delay in IZE onset up to 320 msec whereas the average QT interval was 280 msec. The effect of heart rate (HR), lidocaine and propranolol on IZE delay was examined. With atrial pacing (AP), an average increase in HR of 32% in 6 normal and 3 denervated dogs during ADCA occlusion resulted in severe IZE delays and ventricular arrhythmias whose average onset was 1.4 min earlier than at control HR (2.8 min with AP; 4.2 min control HR). The effect of lidocaine (10-15 mg/kg) during 14 temporary occlusions of the ADCA in 10 dogs was compared with 19 occlusions without lidocaine in the same dogs. At the same period of ischemia there was no difference in IZE delay with or without lidocaine (70±20 msec and 69±20 msec, respectively. Propranolol slowed the average HR from 140/min to 109/min. Average IZE delay at the same period of ADCA occlusion was 42±8 and 49±6 msec with and without propranolol, respectively. ADCA occlusion for the same period with AP at 170-200/min resulted in IZE delays of 66±5 msec without, and 76±2 msec with propranolol. IZE delay and ventricular arrhythmias after ADCA occlusion occurred earlier if HR was increased. Propranolol inhibited the onset of IZE delay by slowing HR. Lidocaine had no effect on HR and did not influence IZE delay or the onset of early ventricular arrhythmias.

EVALUATION OF ACUTE MYOCARDIAL INFARCTION WITH TECHNETIUM-99m-TETRACYCLINE INFARCT IMAGING
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Tetracycline binds to necrotic tissue; its fluorescence has been used to identify experimental acute myocardial infarction (AMI). When Tetracycline is labeled with Technetium-99m (^{99m}Tc-TC), its concentration in the infarcted tissue can be imaged by noninvasive external means, permitting detection, localization and sizing of the lesion. The thorax was imaged in anterior, LAO and RAO projections in 13 CCU and 8 control patients 4, 8 and 24 hours after injection of 20mCi of ^{99m}Tc-TC. Abnormal activity was localized with a radionuclide angiocardiogram ($^{99m}TCO_4^-$) performed immediately after ^{99m}Tc-TC imaging. All controls had negative scans. By clinical criteria, 9 CCU patients sustained AMI, (7 transmural, 2 nontransmural), in 3 the diagnosis was equivocal and in 1 AMI was ruled out. The scan was positive in 9/9, 1/3 and 0/1 patients, respectively. Positive scans returned to normal within 1-2 weeks in 8/9 patients. A negative scan became positive in 1 patient who developed AMI in-hospital. The technique differs from K^+ analogue scanning for infarct detection because: a) ^{99m}Tc-TC produces a positive image which can be analyzed for intensity and size, b) ^{99m}Tc-TC binds to acutely necrotic tissue and therefore does not image areas of old infarction or fibrosis, and c) sequential daily imaging permits temporal analysis of the infarct. In conclusion, ^{99m}Tc-TC permits localization and accurate detection of acutely infarcted myocardium.

HEMODYNAMIC ASSESSMENT OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION (TAPVC) FOLLOWING CORRECTION DURING INFANCY
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Nine patients with TAPVC and pulmonary artery hypertension (PAH) who survived open heart correction prior to 6 months of age, have been followed for one to 6 years after surgery. Five of the infants had supracardiac TAPVC; 3 had drainage into the coronary sinus and one had a mixed type of venous connection. Postoperatively, all of the children were asymptomatic and displayed normal growth and development. Chest x-rays revealed normal heart size and pulmonary vascular pattern in 8 patients, whereas mild cardiomegaly was noted in one instance. Electrocardiograms showed frontal QRS axes ranging from 80° to 105° with mild right ventricular conduction delays. Regression of preoperative right ventricular hypertrophy was apparent in each case. Ectopic atrial pacemakers with heart rates in the range of 85 to 120 were present in 2 patients.

Seven patients underwent post-operative cardiac catheterization 10 months to 5 years (mean =3 years) after surgery. Pulmonary artery pressures ranged from 16/8 to 32/12 (mean=23/10, $\overline{16}$). One patient had an elevated pulmonary artery wedge pressure (14 mm Hg). Two infants had small L→R shunts (1.3/1; 1.4/1), in the area of the coronary sinus, and one had a catheter patent interatrial communication. None had R→L shunts. In each patient, angiography revealed the site of the common pulmonary vein-left atrial (CPV-LA) junction to be widely patent with a normal sized left atrium and left ventricle. This study indicates that successful corrective surgery for TAPVC with PAH by open CPV-LA anastomosis performed in infancy, results in an excellent long term prognosis.

ACTIVITY OF A MYOCARDIAL DEPRESSANT FACTOR AND ASSOCIATED LYSOSOME ABNORMALITIES IN EXPERIMENTAL CARDIOGENIC SHOCK

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It has been reported that a myocardial depressant factor (MDF) accumulates in plasma during various forms of circulatory shock. The present study was undertaken to clarify the properties and significance of this factor in cardiogenic shock. The experimental shock model was produced in dogs by embolization of left coronary artery with metallic mercury. MDF was isolated from the plasma ultrafiltrates on gel-filtration column chromatography, and determined under controlled assay condition. MDF recovered in the chromatographic fraction of molecular weight range between 800 to 1000, gave a positive ninhydrin test and appeared to be small peptide(s). MDF activities increased concurrently with progression of the shock states, reaching to 30 ± 3.2 units and 61 ± 5.9 units at three and five hours after coronary embolization , respectively (mean value ± SE, n = 12, $P < 0.001$). The pre-embolization control samples processed in the same manner yielded no or little MDF which was virtually devoid of myocardial depressant activity (0 ± 1 units, n = 6). Correlative electron microscopic, cytochemical examinations of the visceral organs revealed striking lysosome abnormalities accompanied with severe ischemic cellular injuries particularly in the pancreas, consistent with the lysosomal involvement in MDF production. The data presented indicate that MDF accumulation in the systemic circulation during cardiogenic shock may contribute to the operating pump failure and lethality of shock.

PROPHYLACTIC AND THERAPEUTIC USE OF TRANSVENOUS PACEMAKERS IN INFANTS AND CHILDREN

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Treatment for symptomatic atrio-ventricular heart block (AVB) often consists of a pacemaker. Though transvenous pacemakers (TP) are commonly used in adults with AVB, their use in pediatric patients is seldom described. This paper presents experience with TP in 18 infants and children. In 4, TP were used more than once. Half the patients had congenital AVB, and the others had acquired AVB. Transvenous pacemaking was employed for short term (1-4 hour) prophylaxis on 9 occasions during catheterization or induction of anesthesia prior to cardiac surgery. On 13 occasions TP were utilized therapeutically for treatment of symptoms related to AVB. Transvenous pacing was accomplished in an infant 3 days of age and in 8 patients less than one year old. TP were introduced into leg veins 17 times, 11 percutaneously. Successful pacing was accomplished in all patients. Long-term pacing was carried out for up to 28 days; the pacemaker was used for more than 48 hours on 10 occasions. Stokes-Adams attacks were eliminated in the 4 patients presenting with syncopal spells. In the 9 patients with congestive failure, the clinical condition was improved in 8. Complications were: 1) one catheter required repositioning after one day; 2) there was one perforation of the right ventricle with no apparent hemodynamic side effects; 3) mild leg edema and superficial wound infection occurred twice. Transvenous pacemaking in infants and children has proven relatively easy to perform and is relatively safe. It should be considered for prophylactic and temporary therapeutic management in patients with AVB.

DISTORTION OF LEFT VENTRICULAR (LV) CHAMBER ANATOMY BY RIGHT VENTRICULAR (RV) VOLUME OVERLOAD (VO).

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In previous studies in our laboratory diastolic LV chamber geometry and symmetry of contraction have been examined quantitatively by means of comparative measurements of volume derived independently from frontal (AP) and lateral (LAT) films of biplane cineangiograms (V_{true}=1.03 Vcalc.$_{AP}$ - 7.7 ml; V true = 0.85 V calc $_{LAT}$ + 5.9 ml). This technique was employed in the present study to characterize LV anatomy in 15 patients with RVVO (13 interatrial shunts, Qp/Qs > 2.0/1, 2 pulmonary valve incompetence), and in 12 patients with congenital cardiac defects not associated with RVVO. In the latter group, normal LV chamber geometry was evidenced by close correspondence of measurements of EDV in AP and LAT films (EDV_{AP} 99.9 ± 14.2 ml; EDV_{LAT} 92.9 ± 13.4 ml, r = 0.96); levels of ejection fraction (EF) in the respective views were also similar (EF_{AP} .65 ± .04, EF_{LAT} .55 ± .04, N.S.), demonstrating that LV contraction was symmetrical. In contrast, in patients with RVVO, EDVs differed consistently in AP and LAT films (EDV_{AP} 158.5 ± 25.6 ml, EDV_{LAT} 81.6 ± 13.7 ml, p<.001), indicating substantial distortion of diastolic LV cavity posture and/or shape. Further, measurements of EF also differed significantly (EF_{AP}.66 ± .02, EF_{LAT} .43 ± .03, p<.001), consistent with asymmetric LV contraction. Of interest, at end-systole, at completion of RV emptying, LVV measurements were similar in the two views (ESV_{AP} 57.9 ± 13.3 ml, ESV_{LAT} 45.5 ± 7.8 ml, N. S.). These observations indicate that sustantial alterations in LV diastolic cavity geometry and in symmetry of contraction occur with RVVO, and may result in significant errors in estimation of LV performance based on single plane measurements of volume or dimensional changes.

INFLUENCE OF HYPERTONIC MANNITOL ON REGIONAL MYOCARDIAL BLOOD FLOW DURING MYOCARDIAL ISCHEMIA IN AWAKE, UNSEDATED, AND IN ANESTHETIZED DOGS

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The influence of mannitol (M) on regional myocardial blood flow (RMBF) was assessed in awake, closed-chest, unsedated (A) and in anesthetized (AN) dogs on right heart bypass (RHBP) during acute myocardial ischemia (AMI). AMI was provided by proximal LAD reversible occlusion. Heart rate was kept constant. RMBF was measured using radioactive microspheres (8 μ). M (25%) was given intravenously either as pretreatment (Pr) or following LAD occlusion (Pt). Serum osmolality increased 23 ± 5 (SE) mOsm with M. Hct, LVEDP, mean arterial pressure did not change significantly (NS) after M in AN dogs but mean arterial pressure increased significantly in A ones ($p < 0.05$). Max LV dp/dt increased with M 189 ± 89 mm Hg/sec ($p = 0.05$) in Pr studies, 125 ± 76 mm Hg/sec (NS) in the Pt RHBP ones, and 214 ± 67 mm Hg/sec ($p < 0.025$) in A ones; dp/dt/p also increased significantly in A ones. Pr with M resulted in significant increases in collateral coronary blood flow (CCBF) to the ischemic area (IA) of the LV of 33 ± 12% ($p < 0.025$), to the ventricular septum (VS) of 50 ± 9% ($p < 0.001$), to the nonischemic portion (NI) of the LV of 46 ± 8% ($p < 0.001$), and of 34 ± 13% ($p < 0.025$) to the RV in AN dogs. Pt M produced increases in CCBF of 30 ± 9.6% ($p < 0.02$), to the VS of 19.3 ± 5.2% ($p < 0.02$), to NI portion of LV of 13 ± 4% ($p < 0.01$), and 24.6 ± 10.6% ($p = 0.05$) to RV in AN dogs. M in A dogs with AMI increased regional coronary flow to the VS 32 ± 10% ($p < 0.05$), to the NI portion of LV 30 ± 9% ($p < 0.02$), and to the total LV 23 ± 8.5% ($p < 0.05$). CCBF increased in IA in 4 of 6 studies (15 ± 9%) but the change was NS. These data suggest that M given Pr and Pt LAD occlusion increases RMBF and improves ventricular function during AMI in both awake, unsedated and anesthetized dogs.

LONG-TERM DURABILITY OF PATENT SAPHENOUS VEIN AORTO-CORONARY BYPASS GRAFTS. Samuel B. Itscoitz, MD; David R. Redwood, MD; Leonard E. Grauer, MD; Robert L. Reis, MD; Edward B. Stinson, MD; and Stephen E. Epstein, MD, NHLI, Bethesda, Md.

The ultimate role of saphenous vein bypass operation (SVBO) in the treatment of coronary artery disease (CAD) depends largely on whether grafts tend to occlude with time. To answer this question we restudied 17 patients (aged 36 to 62 years; avg, 49) who underwent SVBO for chronic severe angina pectoris. Patients were selected if they had patent grafts demonstrated at early postoperative study (3 to 9 mos postoperatively). One additional patient (25 years of age) was studied who had SVBO 6 years previously for anomalous origin of the left coronary artery. The 17 CAD patients had a total of 26 grafts patent at early postoperative study: 18 grafts were widely patent with good distal run-off, 5 were widely patent with slow distal run-off, 2 had stenoses at the coronary anastomosis (one mild, one severe with poor run-off), and one had minor luminal irregularities. Late postoperative study was performed 15 to 36 mos (avg 21 mos) following SVBO for CAD. Twenty-four of the 26 grafts were unchanged. One patent graft with good run-off developed minor luminal irregularities; the graft with severe stenosis at the coronary anastomosis had occluded. In the patient with anomalous left coronary artery, a widely patent graft with good run-off was found 4 months postoperatively. Restudy 4.5 years later revealed no change in the appearance of the graft. These results suggest that vein grafts, which within 3 to 9 months following SVBO are widely patent and have good run-off, are anatomically and functionally stable during the ensuing one to 4 years. Their history subsequent to this awaits further definition.

DETECTION OF MITRAL REGURGITATION BY DOPPLER ECHOCARDIOGRAPHY
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A range-gated pulsed Doppler flowmeter, with a 2x4 mm teardrop-shaped sample volume, was used to detect the presence or absence of mitral regurgitation (MR) in 58 sequential patients that underwent left heart catheterization and angiocardiography. Using the A-Mode display, the sample volume was positioned within the left atrium (LA), and at least 3 separate flow readings were obtained before MR was excluded. In MR there is a harsh systolic jet that sounds like steam escaping from a high-pressure pipe. Two of the 58 patients were excluded due to very poor ultrasound penetration, and 4 were excluded due to uncertainty concerning their catheterization results. In the remaining 52 patients, there was a negative Doppler study in 24, which consisted of 20 with no MR at catheterization and 4 false negatives, 3 of whom had minimal to mild MR and one with moderate MR. The other 28 patients had a positive Doppler test, and at catheterization 26 had clearcut MR and 2 had MR only with premature ventricular contractions. These latter 2 patients may be either false positives or may indicate that the Doppler test is very sensitive. This technique provides an indirect method for localizing the origin of cardiac murmurs, and in some patients makes further diagnostic studies unnecessary.

CORONARY HEMODYNAMICS, AND MYOCARDIAL PERFUSION AFTER REESTABLISHING CORONARY FLOW IN EXPERIMENTAL MYOCARDIAL INFARCTION
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To determine the effect of varying periods of ischemia on coronary hemodynamics and regional myocardial flow, both phasic left circumflex coronary artery (LCCA) flow and regional myocardial flow using the radioactive microsphere (8-10μ) method were utilized in 3 groups of chronically prepared awake dogs: I, 60 minutes occlusion of the LCCA (n=6); II, 3 hours occlusion of LCCA (n=13); and III, 24 hours occlusion of LCCA (n=5). The aortic pressure, phasic LCCA flow and the electrocardiogram were monitored continuously before, during and after LCCA occlusion. Inner and outer regional myocardial flow were determined before (control) and during occlusion, 15 minutes after reestablishing LCCA flow, and 26 hours after occlusion. LCCA flow after releasing the snare was significantly increased in all dogs. Both coronary flow and hyperemic response to 20 second LCCA snare returned to normal in 30-60 minutes. During occlusion, the flow in the infarcted region was higher ($p<.001$) in the epicardial region (33$\pm$3% of control) than in the endocardial region (9$\pm$2%). 15 minutes after reestablishing flow, the infarcted region flow was significantly ($p<.01$) higher than control in groups I, II, but was significantly ($p<.001$) reduced in group III (22$\pm$15%). In group II the endocardial flow after releasing the snare decreased significantly ($p<.01$) from 137$\pm$6% to 37$\pm$8% 23 hours later and was not different from endocardial flow in group III. These data indicate that the histological changes produced by 3 hours of myocardial ischemia severely limits future myocardial perfusion, even if flow is reestablished after the initial ischemic period.

DOES RESTORATION OF BLOOD FLOW PRESERVE ACUTELY ISCHEMIC MYOCARDIUM? James Kane, MD; Marvin Murphy, MD, FACC; Joe Bissett, MD; James Doherty, MD, FACC; Karl Straub, MD. VA Hospital & Univ of Ark Med Center, Little Rock, AR.

Surgical intervention with bypass grafts has been advocated as treatment for acutely ischemic myocardium. The purpose of this study was to determine the length of time myocardium remains viable as measured by mitochondrial function after acute coronary occlusion and whether restoration of blood flow would salvage ischemic muscle. The left anterior descending coronary artery was occluded at its midportion in 27 pigs and then released at intervals varying from 15 minutes to 3 hours. One group of animals had a permanent ligation. The ischemic zone and blood flow were estimated by gross inspection, epicardial ECGs, vital dye stain, distribution of ^{3}H digoxin, and flow probe studies. Two hours after ligature release the beating heart was removed and a mitochondrial pellet prepared from ischemic and non-ischemic LV. Oxygen consumption, respiratory control ratio (RCR), and ADP/O were measured with malate and glutamate substrates. Results for ischemic tissue are expressed as a percentage of the control (glutamate):

LIGATION TIME-min	O_2 CONSUMPTION	RCR	ADP/O
15-30	68.4±11.6	97.9± 7.9	95.5± 3.0
60	29.4±19.6	62.6±16.8	92.2±13.0
120	25.6± 8.4	47.8±11.8	96.2± 9.6
180	9.6± 4.1	43.8±30.5	94.2±22.3
180-no release	19.4± 2.0	17.3± 4.2	72.3± 5.3

The results show marked impairment of mitochondrial function in the ischemic zone. The defect appears to be a block in electron transport (state 3 respiration) rather than uncoupling of oxidative phosphorylation and was not reversed by restoration of blood flow. The results suggest that irreversible myocardial damage occurs during the first 1-3 hours of coronary occlusion.

THE GENESIS AND NATURAL HISTORY OF THE SYSTOLIC MURMUR OF SAPHENOUS VEIN AORTO-CORONARY BYPASS TO THE LEFT ANTERIOR DESCENDING CORONARY ARTERY

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The systolic murmur (M) of saphenous vein aorto-coronary bypass (ACB) to left anterior descending coronary artery (LAD) was studied with an experimental, Hewlett-Packard recorder that synchronously averaged demodulated cardiac sound. M was recorded from the surface of an ACB in both surgery and the animal laboratory. M was obliterated by momentary distal graft occlusion. No M was detected from the surface of the aorta. Fifty-two pts with no preoperative M were recorded serially 3 to 15 months postoperatively. In 11 pts with ACBs to coronary arteries other than LADs, no M appeared. Twenty-four of 41 pts with ACB to LAD developed M. There was progressive diminution or disappearance of M with time. Of 10 pts with M followed for a year, M disappeared in 8 and diminished in 2. All pts with M at the time of ACB revisualization had patent grafts, as did the majority of those without M. We conclude that M is produced by systolic flow through ACB, persistence of M predicts graft patency, and absence of M has no predictive value. M diminution with time may reflect a change from turbulent to laminar flow.

LONG TERM FOLLOW UP WITH INTERNAL MAMMARY ARTERY BYPASS

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Between January 1969 and August 1973, 529 internal mammary coronary artery bypasses were performed in 355 patients including single and double bypasses. In 137 patients requiring triple bypass the third bypass was a saphenous vein. Operative mortality during the past 3 years has been 1.7%. Seventy nine internal mammary (IMA) bypasses and 21 saphenous vein grafts (SVG) were studied in 52 patients 12 to 36 months after surgery for a patency rate of 97% for IMA and 81% for SVG. Blood flow was measured in 40 patients with 62 IMA bypasses and 10 SVG. The flow in IMA bypasses ranged between 20 to 135 cc per minute, an average of 61 cc per minute. The blood flow in 10 SVG ranged between 32 to 145 cc per minute, an average of 91 cc per minute. The average velocity flow in 62 IMA bypasses was 20 cm per second and for 10 SVG, 14 cm per second. Average velocity flow was also determined in the normal right coronary artery of patients without coronary artery disease. This was found to be 27 cm per second. Velocity is believed to be an important hemodynamic factor in relating blood flow to thrombus. Maximum flow velocity occurs through the graft when its diameter is equal to or only slightly larger than the artery to which it is anastomosed, assuming the absence of significant distal disease and obstruction. This can best be achieved by using the IMA rather than a SVG in the distal coronary anastomosis. The lower velocity in vein grafts tends to cause sluggishness of flow with a higher incidence of late thrombosis. Reactive hyperplasia also has not been seen with IMA bypasses.

LIMITATION OF CORONARY ANGIOGRAPHY AS A CRITERIA TO BYPASS SURGERY

Earle B.Kay.MD,FACC; H.Naraghipour,MD,FACC; R.A.Beg,MD; M. DeManey,MD,FACC; A.Tambe,MD,FACC; H.A.Zimmerman,MD, FACC: St.Vincent Charity Hospital, Cleveland, Ohio.

Coronary angiography, ventriculography and ventricular function studies are essential in cardiac evaluation of a patient with coronary artery disease being considered for bypass surgery. These studies have certain limitations. A non-visualized artery does not necessarily mean that a suitable vessel is not present to which a bypass anastomosis may be performed. Nor does a highly obstructed vessel proximally with only faint visualization of a narrow distal coronary artery mean distal disease rather than a poorly perfused artery. Nor does an acontractile or even a paradoxical area of the myocardium necessarily indicate that such an area is destroyed. Such responses may be the result of ischemia alone, particularly if the patient complains of angina. This study presents a broup of 50, out of 305 patients operated in the past 2 years, in whom distal coronary arteries were not visualized or so poorly visualized by either antegrade or retrograde flow that by previously accepted standards they would have been denied myocardial revascularization by bypass technics. These patients at the time of surgery had entirely satisfactory distal vessels to which adequate anastomoses were performed. Functional bypasses were corroborated by postop angiograms. Postop flow studies (over one year) were obtained in the majority of the group. Acontractile or paradoxical areas of myocardium as noted by ventriculography were inspected by cardiotomy. In approximately 50%, failure of contraction was due to ischemia which improved following restoration of the coronary circulation.

AN INTRACARDIAC GANGLIONIC DEPRESSOR REFLEX

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Many reflexes arising from the heart have been described. All such reflexes are apparently mediated through central connections of the autonomic nervous system. It is the purpose of this presentation to describe a negative inotropic reflex that is strictly intracardiac in nature. Acute experiments were performed on 13 anesthetized open chest dogs. Strain gauge arches were sutured onto both atria and both ventricles. Arterial blood pressure and lead II ECG were recorded. One to twenty micrograms of acetylcholine injected into a pulmonary vein induced marked decrease in left and simultaneously right atrial contractile force within 2 seconds without change in heart rate. Injection of acetylcholine into the superior vena cava induced a decrease in right atrial force only. To eliminate circulatory effects and possible central nervous system modulation, the vagus nerves and stellate ganglia were sectioned and the animal placed on total cardiopulmonary bypass. Acetylcholine injected into a pulmonary vein still induced a decrease in left atrial and simultaneously right atrial contractile force. Acetylcholine into a pulmonary vein of a dog which had undergone total preganglionic cardiac denervation induced similar changes indicating that this reflex is mediated by an intact parasympathetic postganglionic mechanism. Intravenous injection of the ganglionic blocking drug hexamethonium blocked the acetylcholine induced atrial depressions. Therefore it is concluded that acetylcholine stimulation of ganglionic cell bodies in the left atrium causes inotropic depression of both left and right atria thru a neural mechanism and acts as a negative intracardiac feedback mechanism in both the innervated and denervated hearts.

FAILURE OF SUCCESSFUL MYOCARDIAL REVASCULARIZATION TO ALTER LEFT VENTRICULAR FUNCTION

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55 consecutive patients with chronic angina pectoris were evaluated with biplane angiocardiography for determination of left ventricular volumes, ejection fraction (EF) and contraction pattern before and a median of 4 months following saphenous vein by-pass surgery. The total group was divided into subgroups based on graft patency and adequacy of revascularization as follows: At least one patent graft, 51 pts. All patent grafts, 40 pts, revascularization of all significant coronary lesions, 24 pts. Functional class improved in 82% of pts. Max treadmill performance showed significant improvement in 42 pts tested ($p < 0.001$). Ischemic ST response reverted to normal in 22/29 (76%) and remained negative in 8 others. End-diastolic volume was unchanged in the entire group, preop 84.7 ml/M^2, postop 81.4 ml/M^2, but was reduced significantly in the 24 pts with total revascularization, preop 80.8 ml/M^2 postop 70.9 ml/M^2 ($p < .01$). End-systolic volume, stroke volume and end-diastolic pressure, did not change following surgery. The mean EF was 50.5% preop and 49.5% postop in the entire group and did not change in any subgroup. Heart rate increased from 76 to 85.7/beats/min. ($p < .001$) in the whole and all subgroups. Cardiac index was normal preop and increased significantly in those pts with total revascularization, 3.19 to 3.30 L/min ($p < .01$). Analysis of contraction patterns revealed 35 unchanged, 10 improved and 10 worse following surgery. No subgroup showed consistent improvement. We conclude that partial or total myocardial revascularization fails to improve LV function in patients with chronic angina pectoris.

THE DISSOCIATION OF THE INOTROPIC EFFECT OF DIGITALIS FROM ITS EFFECT ON ATRIOVENTRICULAR CONDUCTION(AVC).

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Sequential changes in left ventricular(LV)contractility and AVC were assessed in open chest dogs(with constant*atrial pacing)during administration of acetylstrophanthidin (AS)IV at 5 minute intervals(.005mg/Kg)until toxic arrhythmias developed. At each interval, a His electrogram, high fidelity LV pressure and its electronic derivative (dp/dt)were simultaneously recorded, and AV refractory period(AVRP)determined by graded trains of single stimuli. Three groups of 5 dogs each were studied:I.autonomic nervous system(ANS)intact(morphine anesthesia)II.ANS blocked (atropine and propranolol)and III.parasympathetic NS blocked(atropine). The linear regression analysis of the results calculated at control and after 25%,50%,75% and 100% of subtoxic dose of AS showed:

Group	max dp/dt	dp/dt 40 mmHg	SH*	AVRP
I	r=0.65	r=0.55	r=0.23	r=0.55
	P<.001	P<.005	NS	P<.005
II	r=0.75	r=0.78	r=-.80	r=0.15
	P<.001	P<.001	NS	NS
III	r=0.56	r=0.73	r=0.10	r=0.69
	P<.005	P<.001	NS	P<.001

Thus, the data indicated 1)dissociation of linearly related effects of AS on LV contractility from its effects on AV conduction(SH)and 2)dependency of AS induced changes in AVRP upon autonomic tone of AV node. Clinically, the data implicate that the dosage and serum level of digitalis required for heart failure may differ from that required for control of supraventricular arrhythmias,the therapeutic response of the latter largely dependent on ANS tone. *Atrial stimulus to His spike interval.

EFFECT OF ARTERIAL PRESSURE MANIPULATIONS ON SEGMENTAL WALL MOTION ABNORMALITIES IN ACUTE MYOCARDIAL ISCHEMIA.

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The effect of alterations in blood pressure (BP) on segmental dyskinesis induced by acute coronary ligation was evaluated in open-chest anaesthetized dogs. Wall motion was recorded by ultrasound reflected directly off the ischemic muscle. Acute ischemia produced characteristic dyskinesis: aneurysmal bulging during isometric contraction and markedly reduced wall velocity (WV) during ventricular ejection. During ischemia the dogs received either methoxamine (M) to elevate BP 25-50% or nitroprusside (NP) to lower BP 25-50%. A control group (C) received no drug during ischemia. NP infusion resulted in improvement in WV (12.7±SEM 1.5 to 18.0±1.9 mm/sec, $p < 0.05$) while M caused WV to decline markedly (13.9±1.9 to 5.8±0.8 mm/sec, $p<0.01$). NP caused little change in aneurysmal bulging during isometric contraction of the ischemic area (3.4±0.2 to 3.2±0.2 mm, p=NS), but M reduced it as the entire ventricle dilated (4.3±0.5 to 2.7±0.7 mm, $p<0.05$). After 1 hour of ischemia the drug infusions were ended, the coronary ligation was released and the ischemic area reperfused. Dogs which had received NP showed more return of wall motion toward the control pre-ischemia state than did the dogs receiving M, but NP was not significantly better than C in this regard.

We conclude that the deleterious effects of increased afterload and/or cardiac depression with M outweighed the beneficial effects of increased coronary perfusion and resulted in more dyskinesis during ischemia and a poorer response to subsequent reperfusion. Decreasing afterload with NP improved wall motion during the period of acute ischemia, but the later improvement with reperfusion was not enhanced.

SUPPRESSION OF OUABAIN-INDUCED VENTRICULAR ECTOPY WITH VERAPAMIL AND REVERSAL WITH CALCIUM

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Verapamil has been shown in vitro to block a slow ionic current carried by calcium and/or sodium, but not block the rapid current carried by sodium. We evaluated the efficacy of verapamil to suppress ouabain-induced ventricular ectopy in open-chested dogs. Lead II and bipolar epicardial electrograms were recorded from atria and ventricles. Right atrium and right ventricle were paced simultaneously at regular intervals for 10 beats, after which a premature ventricular stimulus was delivered or pacing suddenly terminated. Ouabain was administered IV in divided doses (total 40-60µg/kg) until a repetitive ventricular response (RVR) regularly followed a single premature ventricular stimulus, and an accelerated ventricular escape (AVE) regularly followed termination of ventricular pacing. Verapamil was then infused IV (10-30µg/kg/min) until RVR and AVE disappeared or their escape intervals were lengthened by approximately 50%. At this point, calcium gluconate or chloride (100mg/min) was infused IV. In 6 control dogs not given verapamil, RVR and AVE escape intervals remained fairly constant at least 3 hours following ouabain administration. In 14/16 dogs, verapamil completely suppressed RVR and AVE or lengthened the escape intervals by approximately 50%. Calcium antagonized the effects of verapamil by restoring RVR and AVE or by shortening their escape intervals in 8/8 dogs. We conclude that verapamil suppresses ouabain-induced RVR and AVE, and that calcium reverses the inhibiting effect of verapamil. Ouabain-induced ventricular ectopy, possibly analagous to transient depolarizations in vitro, may be due to transmembrane calcium flow of the slow current.

VENTRICULAR TACHYCARDIA AND VENTRICULAR EXTRASYSTOLES DURING THE LATE RECOVERY PHASE OF MYOCARDIAL INFARCTION

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In order to determine the relationship between early premature ventricular contractions (PVCs) and ventricular tachycardia in patients recovering from myocardial infarction, we evaluated 141 patients serially with 10 and 24 hour Holter recordings obtained at monthly intervals. Patients were studied 2 weeks to 18 months after myocardial infarction. Tapes were scanned manually to detect: 1) PVCs, 2) early PVCs on the T wave of a preceding normal complex, and 3) complex ventricular dysrhythmias. Each tape was categorized as follows: 0, no PVCs; 1, < 10 PVCs/hr; 2, ≥ 10 PVCs/hr; 3, multiform PVCs; 4, couplets; 5, ventricular tachycardia. The distribution of classification was 0, 37%; 1, 19%; 2, 9%; 3, 26%; 4, 8%; and 5, 2%. Ninety-one % of the patients exhibited VPCs on one or more tapes. Sequential monthly tapes from the same patient yielded the same classification or differed by only 1 class in 75% of pairs analyzed (486/644). Thus, patients exhibited relatively constant types of ventricular dysrhythmias. Seven percent (56/845) of tapes and 27% (38/141) of patients exhibited at least one early PVC. The frequency of early PVCs was independent of both time after infarction and Lown classification. Ventricular tachycardia was observed 19 times in 14 patients. It was initiated by an early PVC only once. These results indicate 1) that ventricular tachycardia occurring during the late recovery period after myocardial infarction is only rarely initiated by early PVCs, 2) VPC patterns are generally stable over time and 3) almost all patients exhibit ectopic ventricular activity late after infarction.

PATHOGENESIS OF THE POST-ISCHEMIC T WAVE ABNORMALITIES

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In myocardial infarction the stage of acute ischemia with ST segment deviation is usually followed by a post-ischemic stage with inverted T wave, prolonged QT interval and prolonged refractory period in the infarcted area. The cause of post-ischemic T wave changes is unknown but unlike other types of T wave abnormality, they persist after isoproterenol (ISP) infusion.

We studied ventricular monophasic action potentials (MAP) obtained by suction electrodes in open-chested dogs 3-10 days after applying an ameroid constrictor to the left coronary artery. At the time of study the ECG showed typical post-ischemic T wave changes with lengthening of the QT interval by 31±9 msec. but no significant change in QRS duration. After recording MAP's from the noninfarcted area (NI) and the vicinity of the infarcted area (I), ISP (2-5 μg) was injected i.v. to observe its effect on the T wave and MAP's. The hearts were then removed and transmembrane action potentials (TAP) were recorded by microelectrodes from I and NI tissues. In 19 experiments MAP duration in I exceeded that in NI by 32±16 msec. This was due to lengthening of phase 3 although phase 2 was shortened. TAP's showed similar phases 2 and 3 changes and decreased overshoot, but no change in resting membrane potential. After ISP infusion, MAP in NI shortened by 15±8 msec. and in I by 17±12 msec. (difference between the shortenings in NI and I MAP, N.S.) and the T wave abnormalities persisted.

We concluded that: 1) post-ischemic T wave abnormalities are caused by lengthening of phase 3 of ventricular AP in the vicinity of infarction, and 2) ISP does not abolish the difference between the ventricular AP durations in NI and I areas, and therefore does not reverse post-ischemic T wave abnormalities.

COMPARISON OF SURGICAL AND MEDICAL TREATMENT FOR OCCLUSIVE DISEASE CONFINED TO THE ANTERIOR DESCENDING CORONARY ARTERY

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This study assesses the long-term course of 53 patients (pts) with angina pectoris, high-grade occlusive disease confined to the proximal anterior descending coronary artery (LAD), and absence of significant left ventricular dysfunction. Twenty-nine pts had saphenous vein bypass grafts to the LAD and 24 were managed medically following coronary arteriography. Two of the surgical pts (SP) sustained a myocardial infarction (MI) postoperatively and one late postoperatively (10%). There was one late death in the followup period (mean 20 mos). Twelve (41%) of the SP are free of angina and 11 (38%) have less angina. Nineteen pts had coronary arteriography postoperatively (mean 9 mos) and patent grafts (PG) were present in 13 (68%). Seven of 13 pts (54%) with PG and 3 of 6 (50%) with occluded grafts were free of angina. Of the 24 pts managed medically, there have been no deaths and one MI (4%) in the followup period (mean 32 mos). Five of the pts (21%) are free of angina and 12 (50%) have less angina. Bypass grafting in pts with isolated LAD disease is more effective than medical therapy in producing complete relief of angina. Isolated LAD disease in the absence of significant left ventricular dysfunction has a favorable prognosis with regard to death and incidence of myocardial infarction. The prognosis is not enhanced by bypass grafting.

LATE RESULTS OF SURGICAL TREATMENT FOR PREINFARCTION ANGINA.

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Although medical therapy provides effective and safe treatment for most acute episodes of preinfarction angina (PIA), the course of patients followed for one or more years has shown a high incidence of myocardial infarction (MI) and death. Comparison of late surgical results is useful. Of 309 patients undergoing coronary revascularization at the Peter Bent Brigham Hospital from January 1971 to August 1973, 32 (10%) met the criteria for PIA. Of these, 23 had the intermediate coronary syndrome, while 9 had crescendo angina. Twelve patients had previous MI. Eleven patients had significant stenoses (>80%) of the main left coronary artery. Three patients had triple vein grafts, 18 double vein grafts, 9 single vein grafts, and 2 had internal mammary artery grafts to the left anterior descending coronary artery (LAD). In 10 patients, endarterectomy of the right coronary artery (RCA) was performed, and in 2, endarterectomy of the LAD. There were no surgical deaths. Three patients sustained in-hospital MI. A mean followup of 15 months was available for 28 patients 6 to 32 months after operation. There were no late deaths. Only one late MI has occurred. Twenty (71%) have excellent results (insignificant angina without medication and return to full occupation); three have good results (mild occasional angina), and 2 have returned to work. Three patients have fair results, and only 2 have persistent severe angina. Eight patients have had repeat angiography with excellent correlation between graft patency and functional status. These data suggest significantly less mortality and morbidity after surgery for PIA.

REGIONAL PATHOPHYSIOLOGIC EFFECTS OF MYOCARDIAL REVASCULARIZATION AFTER ACUTE CORONARY OCCLUSION

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The effects of coronary reperfusion (R) after 3 hours of LAD occlusion were determined in 7 closed chest dogs. Global and regional myocardial metabolism (M) and hemodynamics (H) were measured during intracoronary balloon occlusion of the LAD and after R. M in both the occluded (O) and nonoccluded (NO) zones were measured simultaneously with H. Significance ($p < 0.05$) is relative to pre-O control (*) and to 3 hours occlusion (†):

		Control	3 Hr O	5 Hr R
Systolic pressure (SP)(mmHg)		136	133	107*
LVEDP (mmHg)		6	11*	6
LV dP/dt (mmHg/sec)		2740	1840*	2270
Cardiac output (CO)(L/min)		3.3	2.3*	2.1*
SV resistance (d.s. cm^{-5})		2720	4365	3640*†
Stroke work (SW)(g·m)		47	34*	17*†
Lactate (A-V)/A	NO	41.0	28.1	22.2*
% extraction	O	38.7	20.9*	-2.9*†
Potassium (A-V) balance	NO	-0.07	-0.14	-0.21*
	O	-0.08	-0.16	-0.22*

Five hours of R caused significant further reduction in SP, CO, SW and SV resistance, as well as marked deterioration of M in O and NO segments in all 7 dogs. Two dogs developed shock. Following R, heart rate increased up to 57%. Arrhythmias developed in 6 dogs. The appearance of Q waves in the ECG and CPK elevations indicated further myocardial damage during R. Histopathologic studies demonstrated hemorrhages, reactive hyperemia, microthrombi and often accelerated necrosis.

These studies suggest that R after 3 hours of occlusion may adversely affect cardiac function and myocardial viability.

THE PROTECTIVE ZONE FOLLOWING ACUTE CORONARY OCCLUSION

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Studies in this laboratory have shown that a second stimulus (S2) delivered during a critical interval following a fibrillatory stimulus (S1) protects an animal against ventricular fibrillation (VF). This critical interval has been called the protective zone (PZ). This study was designed to evaluate the PZ following coronary occlusion. Ten mongrel dogs were anesthetized with alpha-chloralose and a balloon catheter was placed around the left anterior descending coronary artery (LAD). Epicardial electrodes (4 dogs) and right ventricular endocardial electrodes (6 dogs) were positioned and heart rate maintained constant at 220 beats/min. The vulnerable period (VP) and PZ were mapped with unipolar cathodal square wave pulses by variably coupling to pacemaker spikes. The PZ was determined by delivering S1 in the midpoint of the VP with stimuli 20 mA above VF threshold. S2 was variably coupled to S1 and the PZ boundaries mapped. The LAD was occluded and the PZ was determined at 0-3 min, 3-6 min, 6-10 min, and upon release. Narrowing of the PZ occurred after occlusion of the LAD whether determined endocardially ($P < 0.001$) or epicardially ($P < 0.05$). Upon release the PZ returned toward control values. Five additional dogs were studied using a 3-stage LAD occlusion and epicardial electrodes. The VP and PZ were determined at 30-60 min and 120-150 min. A significant constriction of the PZ ($P < 0.01$) and lengthening of the VP ($P < 0.05$) occurred at 30-60 min. At 120-150 min both the VP and PZ had returned to control values. The lengthening of the VP duration and coincident abbreviation of the PZ may be factors contributing to the emergence of VF following coronary occlusion.

CONCEALED INTRAVENTRICULAR CONDUCTION (CIVC) IN THE HUMAN HEART.

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Partway (concealed) penetration of supraventricular or ventricular impulses into the intraventricular conduction system has been demonstrated in animal experiments and also occurs in the human heart. However, its numerous manifestations in clinical electrocardiography as deduced from its aftereffects, in a manner analogous to concealed A-V conduction, have not as yet been systematically evaluated. The following classification of CIVC is proposed, based on the direction and timing of the impulse and the presence of unidirectional bundle branch block (BBB): (A) Transseptal retrograde CIVC, responsible for 1) perpetuation of functional BBB and aberrant ventricular conduction (AVC), 2) alternation of AVC in supraventricular bigeminy, 3) normalization of intraventricular conduction with acceleration of rate in bradycardia-dependent BBB, and 4) prevention of the manifestation of Wenckebach periods in a bundle branch or fascicle. (B) Antegrade CIVC, responsible for 1) prevention of expected AVC when a short cycle follows a long one, and 2) exceptions to the "rule of bigeminy." (C) Retrograde CIVC of a ventricular escape in association with unidirectional bundle branch or fascicular block, responsible for 1) resumption of A-V conduction in "paroxysmal A-V block" with BBB, and 2) facilitation (supernormality) of A-V conduction in type II A-V block due to bilateral BBB. (D) CIVC of a premature ventricular impulse, responsible for 1) initiation or termination of a reentrant ventricular tachycardia, 2) resetting of an idioventricular pacemaker, and 3) pseudo-intraventricular or pseudo-A-V block. Representative examples in clinical electrocardiography will be demonstrated.

TRANSMEMBRANE POTENTIALS IN THE HIS BUNDLE AFTER CORONARY OCCLUSION

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In the first four hours after occlusion of the anterior septal coronary artery, 9 dogs developed bundle branch block and/or heart block. The hearts were excised and preparations dissected to include the His bundle (Hb) and bundle branches. Eight uninfarcted dogs were similarly prepared for comparison. In the Hb and most proximal bundle branches resting potentials (RP) were reduced and diminutive action potentials (AP) had slow upstrokes often with notches or steps. AP sometimes showed distinct rapid and slow components. In more severely affected cells refractoriness had a time-dependent component which outlasted the AP resulting in a departure from voltage-dependent behavior. Encroachment upon this time-dependent refractory period resulted in further diminution of upstroke velocity and amplitude of the AP and progressive prolongation of foot potentials in a Wenckebach periodicity (WP). AP recorded proximal to the site of delay showed late humps during WP. Rapid stimulation could produce repetitive decremented AP and repetitive block (paroxysmal block). Mobitz II block was rarely observed. Automaticity in the Hb was not enhanced and pacemaker function was disturbed. The threshold potential was not constant during phase-4 and pacemaker potentials sometimes were intermittently diminutive resulting in intermittent failure to propagate ("generator dysfunction")- the electrophysiological correlate of concealed escape. There was functional dissociation of nearby cells so that electrotonic interaction might occur while propagation was blocked. Electrotonic interactions could influence pacemaker firing by summation. In summary, ischemia resulted in disturbance in conduction, automaticity, and cell interaction in the Hb.

THE ANATOMIC BASE OF LEFT BUNDLE BRANCH BLOCK

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The anatomic base of left bundle branch block (LBBB) is at present disputed. Accordingly the entire conduction systems of 8 hearts diagnosed electrocardiographically as having LBBB were studied histologically by serial section.

In all cases total or subtotal destruction of the connection between the left main bundle and the bundle of His was found. Pathologic change in the left bundle branch (LBB) more distally was also present. There was no difference in histologic findings between cases with and without left axis deviation. Pathologic change in other parts of the conduction system was not constant.

Five cases had severe atherosclerotic narrowing of 3 main coronary arteries, 1 of 2, and 1 of 1 coronary artery. All 7 of these cases had old and 5 had recent infarction, both anteroseptal and posteroseptal. Two were associated with hypertension in addition. The eighth case had rheumatic heart disease.

This study therefore shows that (1) there is an anatomic base in the conduction system in most if not all cases of LBBB, (2) the lesions found are in the main left bundle or predivisional and (3) the lesions are pathogenetically both ischemic and mechanical. The mechanical factor is related to the vulnerability of the beginning of the LBB to mechanical stresses at the summit of the ventricular septum, exacerbated by hypertension, sclerosis of the left side of the cardiac skeleton, and by infarction of the septum.

DIFFERING EFFECTS OF PROPRANOLOL, DIGOXIN AND COMBINED THERAPY IN PATIENTS WITH ANGINA PECTORIS

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Using a single blind protocol, we treated 15 stable angina pectoris (AP) patients (pts) for 2 weeks with propranolol (P, 160 mg/day), digoxin (D, 0.5 mg/day) and P plus D. This sequence was preceded and followed by 2 weeks of placebo therapy. The radiographic left heart dimension (LHD), treadmill exercise response, and mean AP attack rate/week (AP/wk) were followed serially. Serum D levels were consistently in therapeutic range (0.5 to 2.0 mg/ml). During P alone, average resting heart rate (HR) decreased from 64 to 54 beats/min ($p<.001$), HR-systolic blood pressure (BP) product at the end of treadmill exercise decreased from 21.0 to 14.7×10^3 ($p<.001$), and LHD increased from 46.7 to 47.9 mm/M^2 ($p<.01$). Thirteen of the 15 pts (5 of whom had impaired left ventricular (LV) function) improved on P, AP/wk decreasing from 17 to 6 ($p<.03$); 3 pts no longer had chest pain with treadmill exercise and no pts developed X-ray evidence of pulmonary venous congestion. With P plus D, resting HR, HR-BP product, and AP/wk were the same as with P alone, but LHD decreased in 9 of 15 pts, despite the persistence of resting bradycardia. D alone decreased LHD and HR-BP product from control values ($p<.05$) but AP/wk increased in 7 of 15 pts (47%) from 5 to 15. In 3 pts with impaired LV function, D decreased AP/wk and in the 5 remaining pts AP/wk was unchanged. We conclude that P produces objective and subjective improvement in unselected AP pts without inducing cardiac failure, despite an increase in LHD. The addition of D often reduces the LHD without diminishing the effectiveness of P in these pts, but when used alone, D can aggravate AP.

NOREPINEPHRINE INFUSION FOLLOWING CORONARY OCCLUSION: ISCHEMIC INJURY LIMITED BY ENHANCED COLLATERAL FLOW

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Norepinephrine (NE) has been used widely for the treatment of cardiogenic shock. However, NE, by raising blood pressure and myocardial contractility, increases myocardial oxygen demand. Unless oxygen supply increased correspondingly, ischemic injury following coronary artery occlusion would be augmented. To evaluate the effect of NE on the balance of supply and demand in ischemic myocardium, measurements were made shortly after coronary artery occlusions in anesthetized, open-chest dogs. Collateral blood flow was measured in 10 dogs by the clearance of ^{133}Xe from 0.01 ml depots of saline injected into the ischemic area; and myocardial injury was indicated by the sum of the S-T segment elevations in epicardial electrograms recorded from multiple sites in 6 dogs. Intravenous doses of NE (20-50 µg/min) which increased contractile force and left ventricular dP/dt 2 to 3 fold, and increased mean aortic pressure by 10%, caused only minor increases in myocardial injury. The local energy balance appeared to be maintained in the ischemic area. Accordingly, NE significantly enhanced collateral flow: the half-time for ^{133}Xe clearance decreased from a control of 2.7 min to 1.6 min ($P<0.05$). In contrast, doses of isoproterenol having similar inotropic effects greatly increased ischemia and decreased clearance. We conclude that the ability of NE to enhance collateral flow counters its effect on myocardial metabolism. The clinical usefulness of NE may depend on the balance of these opposing effects.

BENEFICIAL EFFECT OF INTRAVENOUS ATROPINE IN THE PREHOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION

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Recent animal studies of experimental myocardial infarction (MI) have suggested that atropine (A) may be undesirable in the presence of acute ischemia. The development of a mobile coronary care system has allowed clinical evaluation of A in the earliest stage of acute MI. Seventy patients (pts) with bradyarrhythmia (BA) defined as any rhythm with HR < 60 were studied. Fifty-six percent were seen within 1 hour of onset of symptoms. The pts were divided according to systolic blood pressure (SBP) and treatment (Rx). Six pts received isoproterenol (I) as well as A. The average dose of A was 0.86 mg (0.4-2.0 mg).

SBP	Rx	n	Mean HR	Mortality
NL	A	23	50 ± 8 (SD)	13%
NL	none	21	53 ± 7	14%
<100 mmHg	A	16	47 ± 10	25%
<100 mmHg	A & I	6	33 ± 9	33%
<100 mmHg	none	4	51 ± 5	75%

In the 16 hypotensive pts treated only with A, 9 were restored to nl BP and HR. The mortality for these pts was only 11%. A HR response >100 occurred in only one treated pt. There were two unexpected episodes of ventricular fibrillation (VF) in the untreated normotensive pts and only 1 in the treated normotensive group. Only 12% of untreated pts had a spontaneous remission of BA. After hospitalization BA recurred in 80% of pts who had initially been restored to normal by A. Thus the tendency for BA in the early phase of MI is persistent. In conclusion, atropine did not affect mortality when BP was normal but may have reduced the incidence of VF. Atropine clearly reduces mortality when hypotension is present.

FACTORS DETERMINING MORTALITY IN THE PRE-HOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION

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Two hundred seventy-four patients with acute myocardial infarction (AMI) seen by a mobile coronary care system were analyzed to determine the major variables influencing mortality. Forty-eight percent were seen within one hour of onset of symptoms. Fifteen had ventricular fibrillation on arrival and of these 53% were long-term survivors. In the remaining 259 the initial systolic blood pressure (SBP) was the most important determinant of mortality.

Mortality According to Initial BP and HR

	HR < 60	HR 61-100	HR >100	TOTAL
SBP < 100 (n = 46)	36%	67%	83%	61%
Normal SBP (n = 123)	15%	11%	26%	18%
SBP >160 (n = 90)	0%	16%	8%	10%
TOTAL	24%	17%	27%	

Chi-squared 2 x 3 contingency analysis showed that the progressively decreasing mortality with increasing BP was highly significant ($p < 0.0005$). Of interest, the presence of ectopic rhythms or heart block (67% of which were treated) did not influence mortality within each subgroup. When the hypotensive group was excluded from analysis, patients seen < 1 hr. after onset of symptoms had a lower mortality (8.6%) than those seen >1 hr. (19.6%, $p = 0.04$). Patients (pts) under age 65 had a lower mortality than older pts (9.5% vs 21%, $p = 0.026$). The group with ↓ BP had a higher incidence of subendocardial MI (40% for ↓ BP, 25% for normal BP, 9% for ↑ BP) ($p < 0.005$) and of peak SGOT values < 100 unit (48% for ↓ BP, 25% for normal BP, and 25% for ↑ BP) ($p < 0.001$). Thus pts with initial ↓ BP have a better prognosis which appears to be related to smaller sized MI.

MECHANISM AND SIGNIFICANCE OF WIDENED QRS COMPLEXES DURING COMPLETE AV BLOCK IN ACUTE INFERIOR MYOCARDIAL INFARCTION.

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35 out of 225 consecutive patients (pts) with acute inferior myocardial infarction (IMI) developed complete AV block. 12 of these had widened QRS complexes (WQRS) in escape beats (EB). 4 pts showed left bundle branch block (LBBB) configuration, 5 right bundle branch block (RBBB) configuration and 3 both LBBB and RBBB in EB. 3 of 7 pts with LBBB in EB showed during second degree AV block also LBBB in conducted beats, after critical lengthening of RR interval. His bundle (H) recordings, made in 5 of 7 pts with LBBB, all showed a H potential preceding the LBBB shaped EB at HV intervals of 45 - 60 msec. These intervals were equal to those measured later after resumption of 1 : 1 AV conduction. Bradycardia dependency of LBBB in EB was demonstrated in 2 pts by H pacing. Ischaemic phase 4 block could have been responsible for LBBB. LBBB occurred exclusively during AV block and not during sinusbradycardia even at slower ventricular rates. In contrast to LBBB, H recordings made in 6 of 8 pts with RBBB, showed in none a H potential preceding the RBBB shaped EB, whereas the RBBB shaped escape rhythm (ER) occurred together with or even dominated the AVJ ER. Our observations revealed that in pts with WQRS during complete AV block in IMI, the site of AV block was always located in the AVJ. WQRS could either be due to an AVJ ER with phase 4 LBBB or to a ventricular ER alternating with the AVJ ER. 2 of 12 pts with WQRS died. There were no significant differences in immediate, 6 months mortality and mean peak SGOT between pts with narrow and with WQRS, suggesting that WQRS during complete AV block in IMI has no prognostic significance.

INCREASED MYOCARDIAL ISCHEMIC INJURY DURING INSULIN INDUCED HYPOGLYCEMIA.

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Increased glucose supply reduces myocardial ischemic damage following coronary occlusion, but the effect of hypoglycemia is unknown. Accordingly, in 6 open chest dogs 2 serial 20 min occlusions of the left anterior descending coronary artery were performed. The first occlusion served as control (CON) and the second was carried out 15 min after regular insulin (INS) administration (2.5-3u/kg i.v.). The extent and severity of myocardial ischemic injury were determined by epicardial electrocardiography 15 min after each occlusion at 12-16 sites on the left ventricle. While blood glucose fell from 76±8(SEM) (CON) to 37±4mg%(INS) ($p<.01$), the average ST segment elevation rose from 3.8±0.9(CON) to 6.3±1.2mV(INS) ($p<.05$) and the number of sites with ST segment elevation>2mV rose from 8±1(CON) to 11±1(INS) ($p<.05$). Heart rate and mean arterial pressure did not change significantly (from 146±11 to 135±5beats/min and from 113±10 to 93±5mmHg, respectively). In 15 dogs with permanent occlusions, ST segment elevation 15 min after occlusion was compared to myocardial creatine phosphokinase activity (CPK) at the same site 24 hrs later. With occlusion alone, logCPK=-0.095ST +1.57(N=95specimens, r=-.8), showing that ST segment elevation reliably predicts subsequent local CPK. In dogs receiving INS starting 30 min after occlusion, CPK was lower than expected in the area which had acute ST segment elevation and CPK depletion extended to 50% (10/20) of specimens predicted by EKG to be normal. Hypoglycemia increases myocardial damage following coronary occlusion, supporting the importance of glucose availability to cellular survival and suggesting the potential dangers of hypoglycemia in diabetic patients with ischemic heart disease.

EIGHT TO TWELVE YEAR FOLLOW-UP OF 100 PATIENTS WITH FIXED-RATE PACEMAKERS.

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This is an 8 to 12 yr follow-up of 100 consecutive patients(pts) with fixed rate pacemakers(P) implanted from 1961-65 for complete heart block(CHB)and Stokes-Adams syndrome(SA). Ages ranged from 6-91 yrs. with 91% of pts.> 58 yrs. Myocardial infarction(MI) or angina pectoris was present in 45, hypertension in 13, valvular disease in 6, congenital disease in 4, unknown cause in 28, miscellaneous in 4. Post P 10 of 49 (20.4%) died of non-cardiac disease (NCD). Av. ages of 27 survivors is 80.2 yrs. There was 1 P insertion in 1961, pt lost to follow-up(LTF) after 4 yrs. In 1962: 3 P were implanted. Death was 3,5, and 8-1/2 yrs respectively post P; sudden death (SD) occurred in 2, acute pulmonary edema(APE) in 1. Av. age of death was 76 yrs. In 1963: 32 P implanted. Nineteen pts died-5 pts lived<1 yr, 8 pts 1-5 yrs, 1 pt 5-7 yrs, 5 pts 7-9 yrs; hospital death(HD) in 2, SD in 8, APE in 3, acute MI(AMI) in 3, runaway P in 1, NCD in 2. Av. age of death was 76 yrs. Five pts were LTF, 2 after discharge (D), 2 after 1 yr and 1 after 3 yrs. Eight of 32(25%) are alive-2>9 yrs and 6>10 yrs. In 1964: 28 P implanted. Eleven died-4 lived<1 yr, 5 pts 1-5 yrs, 1 pt 5-7 yrs, 1 pt 7-9 yrs; HD in 1,SD in 5, AMI in 1, runaway P in 1, NCD in 3. Av. age of death was 73 yrs. Ten were LTF-5 after D, 2 after 1 yr, 1 after 2 yrs, 1 after 4 yrs, 1 after 6 yrs. Seven of 28(25%) are alive> 9 yrs. In 1965: 36 P inserted. Sixteen pts died-six lived<1 yr, 6 pts 2-5 yrs, 2 pts 5-7 yrs, 2 pts 7-9 yrs; SD occurred in 7, HD in 1, AMI in 3, NCD in 5. Av. age of death was 69.5 yrs. Eight pts were LTF-3 after D, 1 after> 1 yr, 1 after 3 yrs, 3 after 4 yrs. Twelve of 36 pts (33%) are alive> 8 yrs. In summary, long term follow-up of pts with CHB and SA indicated that P implantation significantly improves hospital mortality and longevity as compared to a previous report of a similar series in this institution prior to P era.

ACUTE EFFECTS OF EXTERNAL COUNTERPULSATION ON THE RELATIONSHIP BETWEEN MYOCARDIAL OXYGEN DELIVERY AND REQUIREMENT IN PATIENTS WITH CORONARY ARTERY DISEASE

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Hemodynamic studies were performed in 22 patients (pts) with stable coronary artery disease (CAD) prior to and during external counterpulsation (ECP). During ECP peak and mean arterial diastolic pressure (ADP) were significantly increased ($p < .01$) by 28 ± 3mmHg and 8 ± 2mmHg (mean ± SEM) respectively. Coronary sinus flow (CSF) measured by continuous thermal dilution in 17 pts averaged 119 ± 16cc/min prior to ECP and 113 ± 13cc/min during ECP. Parameters measured which relate to myocardial oxygen requirement were: left ventricular stroke work index (LVSWI) which increased 4 ± 3%, the product of peak arterial systolic pressure and heart rate (double product) which increased 1 ± 3% and pulmonary capillary wedge pressure (PCWP) (10 pts) which fell 1.6 ± 0.8mmHg. None of these changes were significant ($p > .05$). Arterial and coronary sinus lactate was measured in 13 pts. Four of seven pts who had abnormal (<10%) lactate extraction (L-Ext) before ECP changed to normal L-Ext during ECP, however two of six pts with normal L-Ext before ECP developed abnormal L-Ext during ECP. These changes in L-Ext during ECP were not correlated with simultaneous changes in CSF, LVSWI or double product.

Conclusion: In pts with stable CAD, ECP increases peak and mean ADP but does not augment CSF, fails to reduce the indices of myocardial oxygen requirement and does not consistently improve myocardial lactate metabolism. Based upon these findings the ability of ECP to acutely reverse ischemia in pts with unstable angina or to limit the size of infarction in pts with acute myocardial infarction remains in doubt.

CONTRASTING PULMONARY BLOOD FLOW PROFILES IN CHILDREN WITH ATRIAL AND VENTRICULAR SEPTAL DEFECTS

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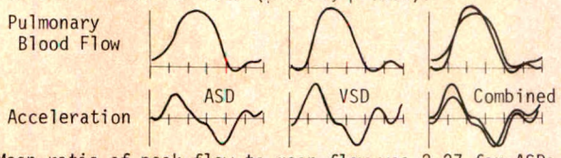
To better understand the difference in pulmonary vascular response to left to right shunts, instantaneous pulmonary artery (PA) flow profiles were studied in 9 children with atrial and 9 with ventricular septal defects (ASD & VSD) at time of defect closure. Groups were comparable in age (4-9 yrs), BSA, and mean PA pressure, flow, and resistance. Parameters related to blood flow and acceleration rate profiles were studied in the time domain; Fourier analysis was used to examine the waveforms in the frequency domain. Average systolic time was essentially the same, ASDs=.34 sec, VSDs=.33 sec. Peak acceleration and flow rates were reached at .07 sec and .17 sec respectively for ASDs and .04 and .13 sec for VSDs ($p=.024$; $p=.036$).



Mean ratio of peak flow to mean flow was 2.27 for ASDs vs. 2.58 for VSDs ($p=.024$); mean ratio of peak acceleration to mean flow was 29.8 for ASDs and 38.2 for VSDs ($p=.06$). Mean normalized flow moduli (modulus/mean flow) of the 3 harmonics were higher for the VSDs. Average difference in phase angle between the 1st and 2nd harmonic was -2.22 radians for ASDs and -1.60r for VSDs ($p=.004$). These differences in profiles of instantaneous PA blood flow in ASDs and VSDs, in spite of comparable mean pressure and flow values, may be a key to understanding the difference in pulmonary vascular response to these two defects.

THE RELATIONSHIP BETWEEN CORONARY PERFUSION PRESSURE, FLOW, AND RESISTANCE IN STENOSED HUMAN CORONARY ARTERIES: THE CRITICAL IMPORTANCE OF SMALL CHANGES IN % STENOSIS.

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Nineteen proximal coronary arteries with varying focal stenoses (2%-98%) were dissected from fresh post mortem adult hearts and perfused with isotonic glycerol saline (n=2.7 centipoise) at constant pressures of 30, 50, 75, 100, 150 and 200 mmHg, while varying the distal bed resistance (r_b) over the range 0.1 to 5 mmHg/ml/min. Flow rate (Q) and arterial segment pressure drop (ΔP) were measured at each perfusion pressure and r_b, and a permanent cast of silicone rubber was made under 100 mmHg pressure following perfusion. Hydraulic resistance ($R=\Delta P/Q$) was proportional to a Poiseuillian scaling ($R_o \alpha 1/r4$) at lowest flow rates (10-30 ml/min), with resistance increasing to 2 or 3 times R_o at higher flow rates (30-100+ ml/min). Curves of flow rates vs. % stenosis showed that flow rate was relatively constant with stenoses less than 70-80%. With a small further increase in stenosis, however, flow rate decreased dramatically. Furthermore, significant reductions in flow rate occurred at lower % stenoses for greater demands (lower r_b). Elastic effects were important in arteries with an eccentric lesion, in that an 80% eccentric stenosis had an additional flow loss of 5% (as compared to a concentric stenosis) when the perfusion pressure was lowered from 100 to 70 mmHg. In conclusion, small changes in % stenosis, perfusing pressure, or increased "demand" (decreased r_b) had dramatic effects on the pressure-flow relationship across focal lesions in human coronary arteries. These results have important implications relative to the quantitation of lesions on coronary angiograms, the alteration of perfusing pressure or changes in myocardial O_2 demand.

IMPROVEMENT IN LEFT VENTRICULAR WALL MOTION ABNORMALITIES AFTER NITROGLYCERIN.

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The effects of nitroglycerin (NTG) on left ventricular (LV) wall motion abnormalities (WMA) were evaluated in 18 patients. Twelve had coronary artery disease (CAD) (70% stenosis of at least one coronary artery) and 10 of these had asynergy while 2 had normal wall motion. Of 6 with normal coronary arteries, 5 had normal wall motion and one had diffuse hypokinesis from a cardiomyopathy. LV cineangiography was performed prior to and 6 minutes after 0.4 mg. of NTG given sublingually. Heart rate increased in all patients (mean 14.5 beats/min) and arterial pressure fell (mean 22 mmHg.).

Asynergy was shown on the initial LV angiogram in 10 of the 12 CAD patients and in 6 of these (5 with hypokinesis and 1 with akinesis) the WMA improved after NTG. In these 6 the ejection fraction (EF) rose (mean 0.15) as did the mean circumferential fiber shortening rate (MCFSR), a mean of 6.0 cm/sec. In the 4 who showed no improvement, the increase in EF and MCFSR were less, averaging 0.05 and 1.6 cm/sec respectively.

One patient with generalized hypokinesis from a cardiomyopathy and no CAD showed no improvement in wall motion, EF, or MCFSR following NTG.

The 7 patients with normal LV wall motion (2 with CAD) showed no change with NTG. Small increases in EF (mean 0.04) and MCFSR (mean 3.8 cm/sec) occurred after its use.

NTG has potential value diagnostically in identifying areas of WMA that may be reversible. It may have value therapeutically in improving LV function.

MAXIMAL CARDIAC OUTPUT BEFORE AND AFTER CORONARY ARTERY SURGERY IN PATIENTS WITH ANGINA

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Oxygen intake ($\dot{V}O_2$), oxygen content of arterial and mixed venous blood ($\bar{A}$-$\bar{V}O_2$), cardiac output ($\dot{Q}$), heart rate (HR), stroke volume (SV), and systemic and pulmonary arterial pressures were measured in 10 angina patients aged 48-63 years, at one minute intervals during multistage exercise to the point of exhaustion. Fifty-seven control (C) measurements of exercise $\dot{Q}$ were made before surgery, and 65 exercise $\dot{Q}$ measurements were made 6 months after surgery (S). All patients experienced relief of angina and subjective improvement in exercise tolerance following surgery. Maximal values (mean and S.D.) were as follows:

Duration (sec) C = 581 ± 112, S = 673 ± 118, P< .01
$\dot{V}O_2$ (L/min) C = 1.534 ± 0.38, S = 1.713 ± 0.56, P< .01
$\dot{Q}$ (L/min) C = 12.84 ± 3.19, S = 13.62 ± 3.60, P< .01
$\bar{A}$-$\bar{V}O_2$ (ml/L) C = 120 ± 13.9, S = 124 ± 19.9, P> .3
HR (b/min) C = 133 ± 12.4, S = 160 ± 16.2, P< .001
SV (ml) C = 97 ± 25.6, S = 85 ± 19.1, P< .001

The data indicate significant improvement in exercise capacity, maximal $\dot{V}O_2$, and maximal $\dot{Q}$ following coronary artery surgery. The marked change in maximal HR may reflect improved coronary blood flow following surgery, while the unexpected but significant decrease in SV might indicate an adverse surgical effect on the myocardium.

CLINICAL SIGNIFICANCE OF TREADMILL EXERCISE INDUCED VENTRICULAR ARRHYTHMIAS

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The incidence of treadmill exercise induced ventricular arrhythmias (EIVA) was studied in 360 patients (pts.) undergoing left heart catheterization and coronary arteriograms (CA) for known or suspected coronary heart disease (CHD). Clinically all pts. had exertional angina or had experienced episodes of chest pain. Only pts. with normal sinus rhythm and no ventricular premature complexes (VPC) at rest were included in the study. All were exercised until the onset of chest pain of their usual day to day intensity or until they reached at least 90% of their predicted maximal heart rate. A dual lead ECG was recorded on magnetic tape and the incidence, frequency and classification of EIVA was determined. The CA were normal in 149 pts. and all were free of evidence of other types of heart disease. The remaining 211 pts. had greater than 50% stenosis of one or more coronary arteries. EIVA were observed in 37 non-CHD pts. (25%) and 80 CHD pts. (38%). Of the 117 pts. with EIVA, 32% were non-CHD pts., 68% CHD pts. Frequent VPC (> 10/min.) were observed in 2% of non-CHD pts., 4% of CHD pts. Exercise suppression of EIVA at progressive workloads and heart rates occurred in 41% of non-CHD pts., 42% of CHD pts. The EIVA were paired or from 2 foci in 30% of non-CHD pts. and 34% of CHD pts. Ventricular tachycardia (VT) and multiple, multifocal VPC were observed almost exclusively in CHD pts. but the overall incidence was only 8% (17 of 211). These data suggest that EIVA do not differentiate between chest pain pts. with CHD and non-CHD except when VT or multiple, multifocal VPC are observed.

RUBIDIUM-81, A NEW AGENT FOR MYOCARDIAL PERFUSION SCANS AT REST AND EXERCISE, AND COMPARISON WITH POTASSIUM-43.

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Although myocardial imaging with potassium-43 (^{43}K) has been established as an effective method for noninvasive evaluation of regional myocardial perfusion both at rest and at exercise, undesirable production characteristics of ^{43}K, limiting its availability, warrant a search for an effective substitute radionuclide. Rubidium-81 (^{81}Rb) is more easily produced than ^{43}K, therefore cheaper and more readily available. This report details our preliminary experience with ^{81}Rb for myocardial perfusion imaging. Rubidium-81 myocardial scanning was performed in 14 patients with coronary artery disease and 1 normal subject at rest, exercise, or both. Rest scans were obtained in anterior and LAO positions after an intravenous injection of 4 mCi of ^{81}Rb; exercise scans were obtained in an identical manner after angina or fatigue had been induced on a treadmill. All patients scanned with ^{81}Rb had myocardial images of diagnostic quality. The myocardial image of the normal subject after exercise was normally homogeneous. Eleven patients had previous myocardial infarction (MI), and all were seen as perfusion defects on rest scans. Seven of these also had exercise scans; four had angina pectoris (AP) and scans showed larger perfusion defects than at rest, three without AP had scans unchanged from rest. Two of three AP patients without MI had normal rest scans and demonstrated perfusion defects after exercise; the third had an equivocal study. Ten patients had ^{43}K scans and in every case the ^{81}Rb image was comparable. It appears that ^{81}Rb, which has significant production advantages over ^{43}K, is an effective substitute for ^{43}K in myocardial imaging.

SUBSELECTIVE PULMONARY ARTERIOGRAPHY WITH BALLOON-OCCLUSION FOR THE DETECTION OF PULMONARY EMBOLISM.

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Subselective pulmonary arteriography employing occlusive arrest of local blood flow by a balloon-tip catheter was evaluated in 18 mongrel dogs. Conventional (main and selective pulmonary) angiograms were obtained in each dog using a Schonander rapid film changer, and a #7 Eppindorf catheter. A second catheter (#5 French end-hole with a 5 cc volume balloon 2 cm from the tip) was introduced and, after balloon occlusion, 5 cc of dye was injected manually through it under fluoroscopy and control pulmonary angiograms obtained. Pulmonary embolism (PE) was produced by injection of thrombin-clots made in vivo. Conventional pulmonary angiograms were repeated; cut-offs (C) and filling defects (D) were identified. Evidence of embolization was then sought by the balloon occlusion technique.

Following dye-injection in the balloon occluded vessel, no wash-out was seen until balloon deflation. C and D seen on conventional pulmonary angiograms were clearly seen at fluoroscopy. Additional C and D were often noted. A single chest roentgenogram was then obtained to document evidence of PE seen at fluoroscopy.

Location of PE was verified at autopsy. No evidence of balloon-trauma or dye-toxicity was observed.

Comparison of conventional pulmonary angiography with the balloon-occlusion technique in this model indicates: (1) diagnosis of PE can be made at fluoroscopy; (2) dye-injection can be reduced by 90%; (3) diagnosis of PE can be documented by a single chest roentgenogram, thus minimizing radiation and (4) there is a better definition of pulmonary vasculature.

THE "RANDOM" NATURE OF TREATMENT SELECTION IN CORONARY ARTERY DISEASE

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This report presents our experience with the medical and surgical management of 700 consecutive patients (PTS) with coronary heart disease. Three hundred forty-eight were treated medically and 352 were treated with aorto-coronary bypass surgery. Two-year survival was the same in the medically treated (83%) and surgically treated (84%) PTS. The comparison of courses of these PTS is valid because treatment selection (TS) tended to be random. The medically treated and surgically treated PTS were compared with respect to 89 baseline characteristics (BC). There were only four statistically significant inequalities in the distribution of BC. These four characteristics did not affect two-year survival. Arteriovenous oxygen difference, the number of coronary vessels with greater than 70% occlusion, and left ventricular contraction were found to be discriminators of survival regardless of TS. These characteristics were used to define subgroups in which surgically treated PTS had a higher two-year survival, in which medically treated PTS had a higher two-year survival, and in which TS did not appear to affect two-year survival. The construction of a clinical information system and the ability to compare cohorts in similar subgroups can thus extend the doctor's ability to manage PTS by allowing him to focus on distant goals.

DISTRIBUTION OF CORONARY ARTERY LESIONS FOUND AT AUTOPSY IN PATIENTS WITH PRE-INFARCTION ANGINA

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Autopsy evaluation of the coronary arteries and left ventricle was undertaken in 21 patients (pts) dying within six months of presenting with pre-infarction angina (PA). Feasibility of premortem saphenous vein grafting SVG was determined.

Evaluating only high grade lesions (>75%), the total distribution of lesions was: 18 in left anterior descending (LAD), 17 in right coronary artery (RCA), 13 in marginal branch of circumflex (M), 7 in proximal circumflex (Cx), 6 in atrioventricular groove vessel, 4 in diagonal of LAD and 2 in the left main coronary (LMC) for a total of 67 lesions.

Criteria for a graftable vessel (G) were taken to be, distal vessel free of severe disease, at least 1.0 mm in diameter and supplying viable myocardium. Results indicated for LAD 12 of 18 vessels G (67%), RCA 13 of 17 G (67%), M 8 of 13 G (61%), Cx 6 of 7 G (86%) and 1 of the LMC vessels was G.

Of the 21 pts only 2 had single vessel disease, both in the LAD and both G. Three pts had only 2 vessel disease, all had at least 1 G vessel. Of 18 pts with 2 or more vessels involved, only 3 had no G vessels.

Therefore, in this group of pts dying following PA, SVG seems feasible in the majority.

CLINICAL LOCALIZATION OF CORONARY OBSTRUCTION BASED ON THE CHARACTERISTICS OF CARDIAC PAIN.

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Analyses of the cardiac pain characteristics in 151 patients, later studied by cinecoronariography, permitted the following conclusions: (1) Localization of the pain in the majority of cases was central (retrosternal) or left sided (precordial or in the nipple area). (2) Pain due to obstruction of the anterior descending artery usually does not radiate. When radiation to the inner aspect of the left arm or to the left epigastrial area is observed, it is suggestive of high-grade proximal arterial obstruction (usually over 90% of the lumen). (3) Pain due to right coronary artery obstruction can be localized and radiate to the right side only or to the right and left sides. The areas of pain in this situation are located in the right hemithorax, the upper limbs, cervical and mandibular regions. (4) In cases of circumflex artery obstruction, the pain radiation depends on the arterial dominance. If the right coronary is dominant, the pain radiates to the left, to the upper limb, neck and mandibule. If the left coronary is dominant, circumflex artery obstruction causes bilateral pain. (5) Pain localization and radiation mutability suggest the incidence of multiple obstructions. (6) There are cardiovascular and nervous system embryologic data supporting the above mentioned findings.

COMPARATIVE ELECTROPHYSIOLOGIC FEATURES OF THE WPW SYNDROME IN THE PEDIATRIC AND ADULT PATIENT.

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The incidence of the WPW syndrome and associated arrhythmias has been reported to decrease with age. The purpose of this study was to determine the electrophysiologic basis for these clinical observations. Four children (ages 6-13; 2 type A, 2 type B) and 16 adults (ages 28-65; 7 type A, 5 type B and 4 type indeterminate) with the WPW syndrome were studied utilizing intracardiac recording techniques. The following observations were similar in the adult and pediatric patient: 1) the mechanism of the onset of tachycardia--a prolongation of the A-H interval and an antegrade bypass block, 2) absence of the delta vector during tachycardia, 3) the induction of tachycardias was observed regardless of the delta vector direction following right atrial premature depolarizations, 5) the AVRP curves, 6) pharmacologic interventions such as Edrophonium, isoproterenol, ouabain, procaine amide, and 7) the P-delta interval. In comparison with the adult, the pediatric patient had 1) a shorter QRS duration; 2) a greater rate of tachycardia; 3) higher incidence of induced tachycardia (4/4 vs 9/16) and 4) shorter V-A, A-V nodal and bypass refractory periods.

In summary 1) these electrophysiologic studies support the clinical observations of a diminished incidence of tachycardias with age, 2) the higher rate during tachycardias in the pediatric patients may be explained by the shorter conducting system refractory periods, 3) the decreased incidence of WPW with increasing age may be the result of the observed prolongation of bypass refractory period in the adult population.

THE EFFECT OF SYSTEMIC ARTERIAL PRESSURE ON COLLATERAL CORONARY FLOW IN MAN.

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The survival of myocardium in the area supplied by an occluded coronary artery depends on the quantity of blood delivered from the adjacent arteries through collaterals and is a function of the richness of the collateral network. However, it is not known how changes in arterial pressure (AP) can affect this collateral coronary flow (CCF) in patients. The methods used to measure CCF in man have been necessarily indirect. However, in patients undergoing aorto-coronary bypass a unique opportunity exists to measure directly the retrograde coronary flow, and the influence of changes in AP. Accordingly, in 6 patients, following the suture of the venous graft to the coronary artery, and before its connection to the aorta, an 18-gauge intracath was placed in the venous graft and the retrograde flow determined directly in a graduated cylinder. AP was raised from 45 to 115mmHg by altering flow in the heart-lung machine from 1000 to 4500ml/min. An increase in AP from 65 to 85mmHg induced an increase in CCF from 16.2±2.2 to 23.2±4.8ml/min ($p<.01$). Thus, an increase in 20mmHg of AP augmented CCF by 48%. One patient showed no CCF and developed a non-fatal infarction postoperative. It is concluded that in each individual the quantity of blood supplied to an ischemic area through collaterals is not only dependent upon the number of collaterals but also upon arterial pressure, thus the latter may play a role in determining the amount of tissue which survives or evolves to necrosis following coronary occlusion.

EARLY REVASCULARIZATION IN ACUTE INFARCTION, HELP OR HAZARD: A RANDOMIZED STUDY

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Recently myocardial revascularization (REVAS) has been advocated in very early stages of acute infarction (MI) to reduce infarct size and complications. The role of maximal REVAS by restoring normal blood supply 2 hours (H) after MI was tested in conscious intact dogs. A previously implanted balloon-cuff around left anterior descending was inflated to produce MI and amongst the survivors it was left inflated in 13 controls (C) for 7 days, it was deflated 2 H following MI in 17. Some of the results of serial studies of LV pressure, its peak dp/dt and dp/dt at developed pressure of 40 mmHg(dp/dt-40), stroke work (SW), ejection fraction (EF) and myocardial O_2 and lactate (L) extraction (EXTR) are tabulated (mean±SEM).

	CONTROL			REVAS		
	2 H	3 H	7 Day	2 H	3 H	7 Day
LVedp mmHg	16±2	17±3	16±2	15±2	15±1	18±2
Peak dp/dtx10^{-2}	19±2	19±3	25±3	18±2	15±2	25±3
dp/dt-40x10^{-2}	16±2	17±3	21±3	16±2	14±2	21±3
SW g.m.	74±4	76±5	97±7	69±4	57±6	69±5
EF %	46±4	44±3	47±4	40±3	45±3	53±2
O_2EXTR %	73±2	70±2	65±3	71±3	59±3	67±2
L EXTR %	11±4	19±3	15±3	18±5	12±5	11±3

Differences between C and REVAS dogs were not significant. Ventricular tachycardia (VT) and dyskinesis developed and persisted in each C and REVAS dog and 23% C(3of 13) and 18% REVAS (3of17) died. The average infarct size was .29 of LV in C, larger (.36 of LV) in 6 of 17 REVAS dogs and smaller (.08 of LV) in 11 of 17 REVAS dogs. Conclusion:Early REVAS fails to prevent VT,death and hemo dynamic,metabolic and angiographic deterioration in acute canine MI and REVAS increases infarct size in one-third.

ULTRASTRUCTURAL FEATURES OF CARDIAC MUSCLE CELLS IN LEFT VENTRICULAR MYOCARDIUM OF PATIENTS WITH CHRONIC AORTIC VALVULAR DISEASE.

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There is no information available on the ultrastructure of ventricular muscle cells of living pts with chronic aortic valvular disease. Therefore, apical left ventricular myocardium was resected at operation from 19 pts with aortic valvular disease and examined by light and electron microscopy. In 10 pts (6 with aortic stenosis, 4 with aortic regurgitation) only hypertrophied cardiac muscle cells and small amounts of interstitial fibrosis were present. In muscle from the other 9 pts (all with aortic regurgitation), however, both hypertrophied and degenerated cardiac muscle cells were observed. Hypertrophied cells demonstrated enlarged nuclei and increased numbers of normally appearing myofibrils, mitochondria, and ribosomes. Most degenerated cells were normal-sized, surrounded by large amounts of interstitial fibrosis and often had lost their connections with adjacent cells. These cells showed loss of normal myofibrillar structure with markedly reduced numbers of thick (myosin) filaments, streaming and clumping of Z band material and disorganization of thin (actin) filaments. The most severely degenerated muscle cells were atrophic with a few or no intact myofibrils. It is concluded that these alterations in the structure of Z bands and myofibrils reflect a degenerative process which probably results from the inability of certain hypertrophied cardiac muscle cells to meet functional demands imposed upon them. Furthermore, these degenerated cardiac muscle cells may be partly responsible for impaired myocardial function in pts with chronic valvular heart disease, left ventricular volume overloading, and congestive heart failure.

REVERSIBILITY OF LEFT VENTRICULAR ASYNERGY ASSESSED BY POST-NITROGLYCERIN LEFT VENTRICULOGRAPHY.

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Left ventricular (LV) angiograms were performed before and after sublingual trinitroglycerin (TNG=0.4 mg) in 22 patients (pts) during routine cardiac catheterization for evaluation of coronary artery disease (CAD). Five pts had no organic heart disease (N). Seventeen pts had CAD with LV dysfunction in the first angiogram; 5 of them had previous myocardial infarction (MI), and 12 of them had angina (AN) alone. Basal (A), mid (B), apical (C) minor axes were measured from LV angiograms. Percentage systolic shortening (PSS) and change in PSS with TNG were calculated for each axis. The results for Group N were as follows:

	Percentage Systolic Shortening			Change in PSS with TNG		
	Mean	SD±	Range (PSS)	Mean	SD±	Range
A	48.3	3.3	(45 to 55)	-0.4	2.8	(-5 to +11)
B	38.2	8.7	(30 to 53)	13.2	6.6	(+6 to +24)
C	48.4	16.5	(38 to 81)	10.25	5.6	(-5 to +57)

Less than 40, 30, and 35 PSS was defined as asynergy and increase in PSS of more than 5, 20, and 25 with TNG was defined as supernormal response for A, B, and C respectively. Five MI pts had 14 asynergetic axes and did not change with TNG. There were 24 asynergetic axes in 12 AN pts; 8 showed normal and 16 supernormal response to TNG. In 4 AN pts reversal of asynergy was total and complete with TNG.
Thus, the post-nitroglycerin left ventriculography is a simple, safe, and useful test to assess the reversibility of left ventricular asynergy in pts with CAD.

METABOLIC DYSFUNCTION OF CORONARY OCCLUDED AND NONOCCLUDED SEGMENTS OF THE HEART

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Studies were designed to determine progressive alterations in regional cardiac function following LAD coronary occlusion in closed chest dogs. Simultaneous lactate (LB) and potassium (KB) balances were determined in both the occluded (O) and nonoccluded (NO) myocardial segments.

During three hours of occlusion, cardiac output (L/min) dropped from 2.70 ± 0.18 (mean ± SEM) to 2.3 ± 0.15, max LV dP/dt (mm Hg/sec) from 2840 ± 135 to 2310 ± 125. LVEDP (mm Hg) rose from 7 ± 0.6 to 11 ± 0.9, and systemic vascular resistance (dynes sec cm^{-5}) increased from 3740 ± 240 to 4270 ± 295. The diastolic phase of pressure distal to occlusion rose from 16 to 18 mm Hg, indicating no significant increase in collateral supply to the ischemic zone within three hours.

Regional metabolic measurements indicated severe dysfunction in O. A significant reduction in LB, from 34.4 ± 2.0 to 23.7 ± 3.1% was noted in NO. This was accompanied by reduction in KB from -.04 ± .02 to -.13 ± .03 mEq/L. Of 34 dogs, NO lactate production was noted in seven and abnormal metabolism in 22. O showed lactate production 17 and abnormal LB in 17. A potassium loss greater than 0.5 mEq/L occurred in O in 11, and in NO in 12 dogs. A 6.8% increase in oxygen extraction in both O and NO was noted following the occlusion.

Serious metabolic derangements are found in the nonoccluded segment following remote coronary occlusion. This finding is related to progressive deterioration of cardiac function which may result in clinical abnormalities such as cardiogenic shock.

PRECATHETERIZATION IDENTIFICATION OF OPERABLE STENOSIS OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY.

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Since left anterior descending coronary artery(LAD) stenosis(>75%:S) is considered specially life-threatening, elective selection of patients(pts) for coronary angio and bypass(CB) would be greatly facilitated if clinical evaluation allowed predictability of these pts suitable for CB. Although previous anterior myocardial infarction (MI) denotes LAD-S, elective CB of LAD is usually not performed with old anterior MI. Thus other criteria are required to identify operable LAD-S. 68 pts with proximal or mid LAD-S without anterior MI had shorter angina duration(2.5 vs 3.6 yrs, $p<.05$) and greater frequency of inferior MI(67% vs 42%, $p<.05$) than 54 proven coronary pts without LAD-S. There were no differences in pt age, sex or presence of risk factors. 52/68(76%) LAD-S pts had operable LAD(<50% distal stenosis). Operability of LAD-S correlated inversely with angina duration and directly with presence of inferior MI(57% vs 36% in 16/68 inoperable pts). Since these data suggested a relation between prior inferior MI to operable LAD-S, an additional 55 pts with inferior MI having coronary angios were evaluated: 26 pts(47%) had operable LAD-S; no factors other than cholesterol >260 mg% indicated operable LAD-S. Thus, despite lack of a relation to most clinical indices, this study demonstrates a predictive value of previous inferior MI and short duration of angina in the precatheterization detection of operable LAD stenosis. Furthermore, a rationale is provided for early coronary arteriographic study of selected pts with prior inferior MI in the detection of high risk LAD-S.

THE EFFECT OF NITROGLYCERIN ON PREMATURE VENTRICULAR COMPLEXES IN ACUTE MYOCARDIAL INFARCTION

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Because of isolated clinical observations suggesting that nitroglycerin (TNG) may eliminate premature ventricular complexes (PVC) during acute ischemic chest pain, a study was designed to assess the effect of TNG on the incidence of PVC in patients with acute myocardial infarction (AMI). 46 patients with AMI were studied. Every other patient was given 1/150 gr TNG q 4 hr sublingually for 24 hr after admission to CCU. PVC were counted for 15 min prior to TNG and for the following 15 min. In the control group PVC were counted for identical time periods. Thus, during any 24 hr period, PVC were counted for 3 hr. The 23 patients receiving TNG had a total of 592 PVC prior to TNG and 276 after TNG ($p<0.005$). The 23 control patients had a total of 408 during the first 15 min period and 525 during the second 15 min period ($p<0.05$). The mean heart rate (HR) before TNG was 79 and 83 after TNG. Average decrease in mean blood pressure (BP) was 10 mmHg. The control group showed no change in HR or BP. Because of the possibility that the slight increase in HR induced by TNG was responsible for reduction of PVC, PVC/min and PVC/beat were calculated. PVC/min and PVC/beat were 39.5 and 0.50 before TNG, 20 and 0.24 for the first 2 min after TNG, 18 and 0.22 for the remaining 13 min of the 15 min period respectively. HR for the 2 min period and the subsequent 13 min were identical at 83/min. The control group had an increase in PVC/min and PVC/beat despite an identical HR of 84/min. This study indicates that TNG decreases PVC in AMI. The mechanism(s) for the TNG effect is obscure. The only significant measurable effect of TNG was decreased BP. This would result in a decreased time-pressure product, possibly improving oxygen requirement/blood flow ratio.

CLINICAL STUDIES AFTER FONTAN'S OPERATION FOR TRICUSPID ATRESIA

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Five children with tricuspid atresia have been operated upon using a modification of Fontan's procedure: Superior vena cava - right pulmonary artery anastomosis, connection of right atrium to pulmonary artery by a graft containing a valve, insertion of a valve in the inferior vena cava at the right atrial junction, tying off the pulmonary artery at its origin and closure of the interatrial communication. Criteria for selection for surgery included normal pulmonary vascular resistance, normal LA mean and LVEDP. LVEDP was 10mmHg in the child that expired. All developed pleural effusion, hepatomegaly, and ascites in the immediate postop period. Three cases who did not have a prior SVC-RPA shunt developed a SVC syndrome which disappeared during the first postop week. Junctional tachycardia and other dysrhythmias were noted during the first 48 hours. Postop studies in three cases showed a marked elevation of right atrial pressure with "ventricularized" tall A-waves, as high as 37mmHg in one patient. All cases showed arterial oxygen desaturation after surgery, 88.5%, 87%, 92%, and 77%. Angiocardiograms showed streaming of dye through multiple sites along the suture line in the atrial septum in all three. A catheter could be passed from RA to LA and into pulmonary veins in all cases. Pulmonary vein desaturation was found in all three cases, severe (82%) in one. Although all 4 survivors were improved by the operation, three of them remarkably so, pleural effusion, right to left atrial shunting, and intrapulmonary shunting have been consistent problems in the early postoperative months.

RELATIONSHIP BETWEEN SEVERITY OF CORONARY ARTERY DISEASE AND ABNORMALLY CONTRACTING SEGMENTS OF THE LEFT VENTRICLE

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Twenty-three patients (pts) were studied two to 24 months following acute myocardial infarction to determine the relationship between the severity of coronary artery disease (CAD) in vessels supplying non-akinetic myocardium and the extent of abnormally contracting segments (ACS) of the left ventricle.

Coronary arteriograms were obtained using Judkins' technique. Both cineangiograms at 60 frames/sec and large roll film angiograms at two to six frames/sec in multiple views allowed precise definition of the arterial lesions. The severity of coronary lesions was scored as 0 = no lesions, 1 = < 50% stenosis, 2 = 50-90% stenosis, 3 = multiple 50-90% stenoses in one vessel, 4 = 90% stenosis, and 5 = 100% occlusion. From left ventricular biplane angiograms exposed at six frames/sec the %ACS was calculated as the ratio of length of ACS to total perimeter of the end-diastolic film. Segments of the left ventricle supplied by each major coronary artery were identified. In four pts with ACS $\geq$ 30%, CAD score to non-akinetic myocardium = 1.5 ± 1.2; in seven pts with %ACS between 16-29%, CAD score to non-akinetic myocardium = 2.7 ± 2.3; in 12 pts with %ACS $\leq$ 15%, CAD score to non-akinetic myocardium = 4.5 ± 3.3.

The inverse relationship between the severity of coronary artery disease in vessels to non-akinetic myocardium and the extent of ACS suggests that collateral circulation stimulated by increasing severity of coronary artery disease may limit the extent of ACS following acute myocardial infarction.

DOES IDIOPATHIC LEFT VENTRICULAR HYPERTROPHY EXIST?

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When left ventricular (LV) hypertrophy occurs in the absence of valvular, hypertensive or infiltrative disease, it may be considered a manifestation of primary myocardial disease. One hundred twenty-eight patients in whom such a diagnosis was made clinically were evaluated. After patients with dilated ("congestive") cardiomyopathy, typical idiopathic hypertrophic subaortic stenosis (IHSS), and family members of patients with IHSS were excluded, 44 subjects remained. All had either the suspicion of LV hypertrophy clinically or met Estes ECG criteria for LV hypertrophy. Cardiovascular symptoms were present in 84%. Echocardiograms were obtained in 39 of 44 patients who were then classified into three groups: asymmetric septal hypertrophy (ASH) (septal thickening present with septal to LV free wall thickness ratio $\geq$1.3); concentric LV hypertrophy (septal and LV free wall thickened equally); and normal (septal and LV free wall thickness essentially equal and each less than 12 mm). Of the 39 subjects with echocardiograms, 33 had ASH, 6 were normal and none had concentric LV hypertrophy. LV mass calculated in the 6 subjects with normal echocardiograms (each of whom had LV hypertrophy solely by ECG criteria) was also normal, suggesting a false positive ECG diagnosis of LV hypertrophy. We conclude that most patients with clinical or electrocardiographic evidence of unexplained LV hypertrophy have either ASH or are normal. Thus, if idiopathic LV hypertrophy (symmetric thickening of both the septum and LV free wall) does exist as a separate disease entity, it must be distinctly uncommon.

EXTERNAL COUNTERPULSATION - A NON-INVASIVE FORM OF CARDIAC ASSISTANCE

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It was previously demonstrated in man that intra-aortic balloon counterpulsation strikingly improves hemodynamics and myocardial metabolism in myocardial infarction shock. We evaluated the effect of non-invasive external counterpulsation (ECP) in acute myocardial infarction (AMI) without shock. Mean values of 13 patients are presented. Studies were performed before ECP, 90 min. during and one hour after termination of assistance. During ECP, aortic peak diastolic pressure averaged 137 mm Hg ($p < .001$). Both, systolic peak and mean aortic pressure fell slightly (5 and 6 mm Hg, $p < .01$). Left ventricular ejection resistance decreased 24%. Cardiac index improved from 1.9 to 2.3 L/min/M^2, $p < .001$, associated with fall of arterio-pulmonary artery oxygen difference from 6.2 to 5.3 ml/100 ml, $p < .01$. Pulmonary artery wedge pressure fell from 18 to 15 mm Hg, $p < .001$; right atrial pressure remained unchanged. Coronary blood flow increased from 82 to 101 ml/100g/min ($p < .05$) and remained improved one hour after termination of ECP. Lactate metabolism, abnormal in 8 patients, improved with ECP (-9 to +14%, $p < .05$). Coronary sinus oxygen tension increased from 23 to 25 mm Hg, $p < .05$. Conclusion: ECP increases diastolic aortic (coronary perfusion) pressure and improves myocardial oxygenation in AMI. These findings indicate that ECP may prove capable of salvaging endangered myocardial tissue.

METABOLIC CHANGES IN ISCHEMIC MYOCARDIUM BY NITROPRUSSIDE

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It was previously demonstrated that nitroprusside has a beneficial effect on the failing heart, decreasing afterload and filling pressure of the left ventricle while improving systemic blood flow and - presumably - myocardial oxygenation. We studied the metabolic effect of nitroprusside on ischemic myocardium in 8 dogs with myocardial infarction. Blood samples were taken simultaneously from the femoral artery, from the local vein draining the ligated left descending coronary artery and from the coronary sinus. Blood was withdrawn before, 15 and 30 minutes after coronary artery ligation and during 15 minutes of continuous intravenous infusion of 3-5 mic g/min nitroprusside. After ligation, left ventricular diastolic pressure rose. The metabolic changes in the venous drainage of the ischemic area were as previously described: myocardial oxygen extraction increased an average of 7%, lactate extraction shifted to production and glucose utilization increased. During nitroprusside infusion, left ventricular systolic and diastolic pressures fell. The response of heart rate varied. The most striking metabolic effects were a change from lactate production (-38%) to extraction (43%) and a decrease of glucose utilization. Myocardial oxygen extraction and coronary venous oxygen tension did not change consistently. Similar, but less conclusive findings were observed sampling mixed coronary sinus blood. Conclusion: These findings suggest that nitroprusside improves myocardial metabolism of ischemic myocardium and thus may be able to decrease infarct size.

METABOLIC EFFECT OF PROPRANOLOL ON ISCHEMIC TISSUE IN HUMAN AND EXPERIMENTAL MYOCARDIAL INFARCTION

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We previously demonstrated in human myocardial infarction that propranolol improved myocardial metabolism of the left ventricle. In order to determine how much of this improvement occurred in the ischemic area, blood was sampled in nine dogs from the local vein draining the ligated left descending coronary artery as well as from the coronary sinus. Samples were taken before, 15 and 30 min. after ligation and 15 and 30 min. after 1.0 mg/Kg I.V. propranolol. The following results were observed draining local venous blood: After ligation, oxygen extraction increased (68 to 75%, $p < .05$), lactate extraction shifted to production (28 to -70%, $p < .05$), and glucose extraction sharply increased (4 to 13%, $p < .05$). Free fatty acid extraction did not change. After propranolol, improved oxygen availability was demonstrated by change from lactate production to extraction (-70 to 4%, $p < .05$) and by decrease of glucose extraction (13 to 10%). Oxygen extraction did not change. Both epinephrine and l-norepinephrine content decreased with propranolol. Similar but less conclusive metabolic changes were observed in mixed coronary sinus blood. Propranolol decreased heart rate an average of 54 beats per min ($p < .001$); left ventricular systolic pressure did not significantly change, while end diastolic pressure rose in average 5 mm Hg ($p < .05$). None of the dogs developed left ventricular failure. Conclusion: These results clearly demonstrate that propranolol improves myocardial metabolism in the ischemic zone and is of therapeutic benefit in certain patients with acute myocardial infarction.

ECHOCARDIOGRAPHIC RECOGNITION OF CONGENITAL BICUSPID AORTIC VALVE

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Fourteen patients (age 7 to 25 years) with bicuspid aortic valve proved by surgery and angiography (10) or angiography alone (4) were studied by echocardiography. Eight of them had aortic valve stenosis, 4 had pure aortic incompetence and 2 were associated with isolated coarctation of aorta. A comparison group of 12 patients (6 with aortic valve disease and 6 without aortic valve disease) who had proved tricuspid aortic valve was also studied. Echocardiograms in tricuspid aortic valve patients showed the closed position of the cusps near the middle of the aortic lumen. In contrast marked eccentricity of the aortic valve cusp echo in diastole could be demonstrated in all with bicuspid aortic valve. The Eccentricity Index (1/2 aortic lumen diameter/minimum distance of diastolic cusp echo from anterior or posterior aortic margin) was low (range 1.0-1.15) with tricuspid aortic valve and high (range 1.5-3.6) with bicuspid aortic valve ($p < 0.001$). This index was not significantly affected following successful valvotomy. In systole, the cusps in bicuspid aortic valve patients opened briskly to the periphery of the aortic lumen so that the valve leaflets appeared markedly asymmetric. Echocardiography is of value in the recognition of bicuspid aortic valve.

INFLUENCE OF LEFT VENTRICULAR FUNCTION ON EARLY PROGNOSIS IN ATHEROSCLEROTIC HEART DISEASE

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Of the 246 men followed for 18 months after study by coronary and left ventricular (LV) angiography, 24 died. Survival averaged 5 months. Surgical deaths were excluded from the analysis.

Evaluation of clinical status, resting electrocardiogram, exercise test, coronary arterial anatomy and both qualitative and quantitative LV function demonstrated that the most striking differences between living and dead groups were in LV studies.

	Living	Dead	P
EDV, cc/m^2	79±24	101±39	<0.0001
ESV, cc/m^2	35±23	60±35	<0.0001
Ejection Fraction	58±15	43±17	<0.0001
Contraction Grade	2.3±1.2	3.3±1.4	<0.0002

Men with diffuse, moderate focal and mild focal contraction abnormalities had mortalities of 37%, 17%, 11% respectively, in contrast to 4% in those with a normal LV contraction pattern. Duration of survival was similar for each group.

For 64 cases with ejection fractions less than 50%, the mortality was 23%. Of the 24 total deaths 20 had ejection fractions below the median of the 246 men.

Thus the level of LV performance is an important determinant of survival even in the absence of surgical therapy.

POST-OPERATIVE BLOOD PRESSURE FOLLOWING COARCTECTOMY IN YOUNG CHILDREN

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We have reviewed all patients who have undergone successful coarctectomy at The Hospital for Sick Children excluding those who were operated on at less than a year old and those with a post-operative follow up of less than 6 months. The mean follow up was 4.3 years (range 0.5-13.5 years). Latest post-operative systolic and diastolic blood pressures recorded in the right arm were compared with the 96th percentile for age. Forty-eight of 187 (25.3%) of the patients were found to have systolic hypertension and 84 of 183 (46%) to have diastolic hypertension. In order to decide whether age at operation influenced the post-operative blood pressure 2 groups of patients were compared. Group I consisted of 22 patients operated on between the age of 4 years and 6 years 11 months and Group II, 20 patients operated on when aged 11 to 13 years 11 months. The mean follow up for Group I was 4.3 years and for Group II was 3.7 years. Diastolic blood pressure was expressed as a percentage of the normal mean diastolic pressure for age and the mean fall in this percentage value compared for the 2 groups using Students T test. There was no significant difference between the 2 groups. A large majority of patients following coarctectomy remain significantly hypertensive raising the question of need for medical hypotensive therapy. Operation early (4-7 years) does not seem to improve the chances of the post-operative pressure becoming normal.

PULMONARY VALVOTOMY FOR ISOLATED PULMONARY STENOSIS: AN ANALYSIS OF 110 PATIENTS TREATED BY THE INFLOW STASIS TECHNIQUE.

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This study assessed the pre and postoperative clinical, ECG, and cardiac catheterization data in 110 patients with isolated pulmonary stenosis (PS) operated between 1961 and 1972 using the inflow stasis technique. The patients ranged in age from 2 days to 36 years, and 11 (10%) were less than 1 year. Operative mortality was 3.6% (4/110), two deaths occurring in infants less than 1 week of age. Preoperative cardiac catheterization was performed in each patient and 69 (63%) had postoperative catheterization. The mean preoperative systolic gradient was 93 mm Hg and calculated pulmonary valve area (PVA) 0.38 cm^2/m^2. Postoperatively, the mean gradient was 23 mm Hg and PVA 1.1 cm^2/m^2. Results were considered good in 78% (<30 mm Hg gradient), fair in 15% (30 - 50 mm Hg gradient),and poor in 7% (>50 mm Hg gradient). Six of 7 patients with pulmonary valve dysplasia had unsatisfactory results, and we now recommend valvotomy on cardiopulmonary bypass when dysplastic PS is suspected. Four patients required reoperation for high residual gradient, 1 of whom had a dysplastic valve. Significant reduction in the QRS/T angle was the most characteristic ECG finding after surgery. Favorable operative results, low morbidity and mortality, and freedom from the problems of cardiopulmonary bypass are cited as reasons for use of this technique in the treatment of isolated pulmonary valvar stenosis.

VENTRICULAR ARRHYTHMIAS ASSOCIATED WITH SUDDEN DEATH IN SURVIVORS OF ACUTE MYOCARDIAL INFARCTION

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A prospective study of the frequency and type of ventricular arrhythmias in ambulatory survivors of myocardial infarction has been made to investigate their relationship to sudden death. Holter tape recordings were obtained at the onset of infarction, at two weeks, at one month, and at monthly intervals thereafter. Eight patients died suddenly, and their arrhythmias are compared with 8 patients who have survived for two years. Holter tapes were analyzed by Argus/H, a unique high speed computer system for automatic identification of premature ventricular contractions. All computer identified PVCs were verified. A total of 103 tapes have been analyzed, representing over 5 million heart beats. Both survivors and sudden death patients had approximately the same high incidence of early PVCs (EPVC) and PVC rates ≥ 10/hr during the acute phase. However, striking differences were noted between survivors and sudden death patients during the early ambulatory phase (2 weeks - 3 months post infarction).

	# Pts	# Tapes	% Pts with EPVC	% Pts with PVC ≥ 10/hr
Survivors	8	28	13	13
Sudden Death	8	22	75	75

These differences are highly significant ($p < .02$). It is concluded that striking differences in early PVCs and PVC rates exist between these surviving and sudden death patients in the early ambulatory phase of recovery which may allow ready identification of patients prone to sudden death.

"SLUGGISH" SINUS NODE SYNDROME AS A PART OF CONGENITAL HEART DISEASE

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Sinus node(SN) dysfunction was suspected in 4 children with congenital heart disease(CHD) who presented with atrial dysrhythmias: junctional rhythm(1 patient),sinus bradycardia with ectopic atrial escape(1 patient), and atrioventricular(AV) dissociation with slow, irregular atrial rate and junctional rhythm(2 patients). One child had paroxysmal supraventricular tachycardia. SN function was evaluated by:(1)submaximal exercise,(2)intravenous atropine(0.01 mg/Kg), and (3)overdrive atrial pacing (OAP) at rates of 120-150/min. Exercise did not change the atrial rate in 1 child and increased it by less than 20% for brief periods in the other 3. Atropine administration resulted in very similar changes in atrial rate and increased the junctional rate in 3. The sinus recovery time after OAP was abnormally prolonged in all (range 900-1240, average 1050). Escape to the His occurred earlier than to the SN in 1 patient. AV nodal function was normal as OAP at different rates produced 1:1 AV conduction with normal atrial-His and His-ventricular intervals. SN dysfunction is the basis for the dysrhythmias in these children, but the etiology is unclear. The association with CHD suggests that it could be a congenital defect of the SN or the effect of prolonged hemodynamic alterations on the SN. The latter seems more likely since all 4 of our patients had pressure or volume overload on the right side. Prognosis is guarded because of possible brady-tachyarrhythmias. This syndrome should be considered in the presence of any atrial dysrhythmia. Exercise and atropine offer a simple way of obtaining supportive evidence.

FIVE YEAR EXPERIENCE WITH A DISC-TURTLE NECK MITRAL VALVE

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The performance of the composite Harken disc valve with Magovern turtle neck cuff (HMDV), inserted by continuous suture technique, has not been described. Between 1968 and 1973 HMDV was implanted electively in 100 patients (pts.). Of these 45 had previous mitral valve surgery and the pulmonary artery systolic pressure was greater than 50 mm. Hg. in 57 patients. The early and late mortalities were the following:

	No. Pts.	Early Mortality %	Late Mortality %
MVR*	79	7.5	6.5
MVR + CABG+	7	0	14.0
DVR‡	14	7.1	14.0
Class III (NYHA)	51	7.8	1.9
Class IV (NYHA)	49	8.1	14.0

*mitral valve replacement, +coronary bypass graft, ‡double valve

Pulmonary hypertension and previous cardiac operations did not influence mortality. In 2168 pt. month follow up there were 7 thromboembolic episodes. Peribasilar leaks were not encountered. Postoperative catheterization in 12 pts. revealed satisfactory hemodynamic function. These results indicate that HMDV is a satisfactory prosthesis and has definite advantages over other widely used artificial mitral valves.

BANDING OF THE PULMONARY ARTERY IN NEW ENGLAND

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Banding of the pulmonary artery has proved effective in decreasing excess pulmonary blood flow and preventing development of pulmonary hypertension in critically ill infants. The New England Regional Infant Cardiac Program experience with this procedure (7/68-6/72) has been reviewed. The overall mortality for banding in 206 infants is 36% including 64 early deaths and 10 late ones. The latter includes those who expired during corrective surgery. Infants with ventricular septal defect (88) represent the largest group; mortality among 48 with simple defects was 8% compared to 42% among 40 with associated lesions. In all infants mortality is appreciably higher when the ductus is interrupted at the time of banding (45 vs. 31%) probably reflecting sicker and younger patients. Transpositions with atrial septectomy have a lower mortality than the group without (38 vs. 47%). Significant improvement in mortality results when the figures are corrected for low birthweight and serious associated anomalies, particularly among those with endocardial cushion defect (Downs). The mortality for banding among infants with essentially uncorrectable lesions is 49% (range 12-80%) with virtually all deaths occurring early. Although the mortality figures for the total group are high and lead one to aim at complete correction at a earlier age, for most of the lesions it should be borne in mind that pulmonary artery banding is still the only palliative procedure for a host of presently inoperable lesions. With further improvement in surgical techniques and post operative management many of the patients successfully palliated may become candidates for corrective surgery.

DYNAMIC RESPONSIVENESS OF DISTANT MYOCARDIUM DURING TRANSIENT ANTERIOR WALL ISCHEMIA

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The regional responses of distant myocardium (DIST) supplied by the left circumflex artery to acute ischemia of anterior myocardium (ISCH) supplied by anterior descending artery (LAD) was studied in 12 open chest anesthetized pigs. Three markers of regional response were used for both areas; a newly-designed, low impedance surface ECG electrode, a force gauge sutured in series with outer wall fibers, and coronary inflow to the region. Flow was measured by electromagnetic flowmeter cuff-probes around the proximal coronary artery of supply, with special care taken in dissection and placement to minimize interruption of vascular innervation. With transient LAD occlusions (15 to 120 sec.) the characteristic rapid decline in contractile force and evolution of surface ECG changes in the ISCH area was almost invariably accompanied by a significant increase in contractile force in the DIST area (91% of 57 occlusions). DIST QRS-T voltage changes occurred less frequently (67% of 30 occlusions). In only 58% of 34 occlusions in which there was an increased DIST contraction, was there a concommitant rise in circumflex coronary inflow. High dose propranolol or phentolamine did not block the DIST responses. When the circumflex artery was cannulated and perfused from the carotid artery the DIST response was obliterated - suggesting interruption of vascular neural fibers by the tight cannulating ligature. The almost uniform finding of overcontraction of DIST normal myocardium during early ischemia is consistent with a reflex homeostatic mechanism for conservation of whole ventricular performance perhaps induced by the abnormal stretch of asynchronous contraction. The absence of a consistent rise in circumflex flow suggests the stimulation of anastomotic inflow.

THE ROLE OF ALPHA ADRENERGIC RECEPTORS IN MEDIATING POSITIVE INOTROPIC EFFECTS IN VENTRICULAR MYOCARDIUM

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It has been traditionally assumed that there are no alpha adrenergic receptors of importance in left ventricular myocardium. In order to evaluate this assumption, dose response curves to alpha agonists and antagonists were obtained in isolated cat papillary muscles studied in vitro. Methoxamine (n=6) produced a 30 and 45% increase in contractile force at doses of 10^{-5} and 10^{-4}M. These effects were unchanged following beta adrenergic blockade with 10^{-6}M propranolol, but were totally abolished by alpha adrenergic blockade with 10^{-6}M phentolamine or ergotamine. Phenylephrine produced the following increases in contractile force: 10% at 10^{-7}M, 30% at 10^{-6}M and 60% at 10^{-5}M (n=8). These effects were not altered by 10^{-6}M propranolol although they were reduced by at least half with alpha blockade by 10^{-6}M phentolamine or ergotamine. This suggests that the effects of phenylephrine were due to both alpha adrenergic and non-adrenergic receptor stimulation. The known positive inotropic effects of isoproterenol were unaffected by the addition of 10^{-6}M phentolamine. The known positive inotropic effects of norepinephrine (n=17) were partially blocked at low doses by 10^{-6}M propranolol and at high doses by 10^{-6}M phentolamine. Parallel measurements of the effects of these agents on myocardial adenyl cyclase activity confirmed that the beta agents stimulated adenyl cyclase activity while the alpha agonists did not increase adenyl cylcase activity. Thus, the present study suggests that alpha agonists have positive inotropic effects on the myocardium in a manner similar to beta adrenergic agents. These effects do not appear to be mediated by stimulation of adenyl cyclase activity.

DIGOXIN EFFECTS ON SINUS NODE REENTRY IN THE DOG

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Using the recently described experimental model for sinus node reentry (SNR) the effect of digoxin (D) was assessed in 10 dogs with extrinsic cardiac denervation (group I) and in five dogs with an intact cardiac nerve supply (group II). In all dogs, before D, after the last basic beat, A_1, a premature atrial beat, A_2, was followed by a sinus node reentrant beat, A_3, when A_2 fell within the reentry zone. Thirty-five minutes (av) after an i.v. bolus (7.5 ug/kg) and infusion (2.5 ug/kg/min) of D, toxicity developed manifest by either increased ventricular and/or ectopic atrial automaticity (14 dogs) or high degree A-V block (one dog in group II). D had relatively little effect on SNR in both groups, and SNR could be demonstrated at the onset of toxicity in all dogs. D delayed the appearance of A_3 during SNR (i.e. increased the A_2A_3 interval) by 40 msec (av for groups I and II) with a maximum delay of 200 msec in one dog in group II. This increase in the A_2A_3 interval which indicated delay along the reentrant pathway did not correlate with atrial refractoriness which increased 14 msec (av; atrial effective refractory period) in group I and decreased 22 msec (av) in group II. In seven dogs that developed increased ectopic atrial automaticity with D, premature atrial stimulation was followed by reentry that appeared to originate from the site of the ectopic atrial focus, and suggested that automaticity per se may predispose to reentry. The knowledge of the relative insensitivity of SNR to D, at least in this experimental model, contrasts with the previously reported sensitivity of SNR to quinidine, and may be important in the management of SNR in man.

EFFECT OF DIGITALIS ON THE RESPONSE OF VENTRICULAR PACEMAKERS TO SYMPATHETIC NERVE STIMULATION

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It is established that digitalis antagonizes the chronotropic effect of adrenergic stimulation of the heart. This finding would suggest that the sympathetic nervous system does not play a significant role in ventricular arrhythmias produced by digitalis. However, this antagonism has been established by testing the response of sinus node pacemakers to digitalis and adrenergic stimulation. Since the clinically significant digitalis-induced arrhythmias are ventricular in origin, the response of ventricular pacemakers seems the critical parameter. To test this parameter, we electrically stimulated the postganglionic sympathetic nerves of 5 anesthetized dogs with complete A-V block using frequencies of 3, 10, and 20 Hz. before and after administration of ouabain (40 μg/kg I.V.). Before ouabain these frequencies increased ventricular rate by 17 ± 4.9, 37 ± 3.7, and 39 ± 3.9 %. After ouabain, ventricular rate increased by 11 ± 5.2, 42 ± 7.0, and 46 ± 4.6 %. Ventricular tachycardia occurred in two of these ouabain-treated animals during stimulation. These results indicate that the chronotropic response to adrenergic stimulation of ventricular pacemakers unlike that of atrial pacemakers is unaffected or enhanced by digitalis.

CORONARY HEMODYNAMIC AND METABOLIC EFFECTS OF PROPRANOLOL IN IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS.

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To clarify the basis for symptomatic improvement following propranolol (P) in patients with idiopathic subaortic stenosis (IHSS) coronary flow as reflected by coronary sinus blood flow, left ventricular (LV)oxygen consumption ($LV\dot{V}O_2$), LV efficiency = LV work index (LVWI)/$LV\dot{V}O_2$, lactate extraction (XL), and LV hemodynamics were measured in 6 IHSS patients at rest and during atrial pacing induced tachycardia before and after P,(10mg). All had resting outflow tract obstruction (mean gradient 56.8 ± 11 mmHg) and normal coronary angiography. During tachycardia induced angina, $LV\dot{V}O_2$ increased,(Rest→pacing, 13.4±2.1→25.2±4.1ml/cc/min) LVWI was unchanged, (9.79±.66→9.66±.71 Kg-m/min/m^2) and LV efficiency declined 35% as XL declined abnormally in 5 of 6 patients. Following P, LV outflow tract gradient was not significantly changed (53.4±16 mm Hg) but $LV\dot{V}O_2$ declined 12% associated with proportional reduction of LV work (9.79±.66→8.92±.58, $p<.05$). At the same pacing rate after P, $LV\dot{V}O_2$ increased much less (+51%, $p<.05$)as LV work was unchanged and LV efficiency declined less (-21%, $p<.05$) then before P. XL increased in each patient compared to tachycardia before P, but outflow tract gradient was unchanged (50±18) and angina did not occur. These data indicate that in some patients with IHSS, P reduces oxygen wasting thereby decreasing LV inefficiency. This effect, independent of changes in outflow tract obstruction, may relate to clinical improvement in patients with IHSS.

THE ASYMPTOMATIC CORONARY PRONE MALE: CLINICAL,CORONARY ANGIOGRAPHIC AND HEMODYNAMIC CORRELATIONS.

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A prospective study of young, high risk subjects who never had symptoms suggestive of coronary heart disease (CHD) was done to identify and characterize the preclinical phase of CHD. Coronary angiographic (CA),metabolic and exercise left ventricular (LV) hemodynamic and ECG studies were performed in 41 asymptomatic males (mean age 36 years) with hyperlipemia and a family history of CHD. Ten had xanthomas (24%), 15 were obese (34%), 18 had hypertension (43%), and 21 had abnormal GTTs(51%), while only 18% had abnormal submaximal exercise ECGs(4 with ST depression ≧ 1 mm and 3 with ST depression = 0.5mm). LV angiography and rest → exercise LV function (stroke work index 83 ± 5.0 → 110 ± 11.0 Gm-m/beat/m^2 and LV end diastolic pressure 10.2 ± 2 → 11.5 ± 2.6 mmHg) were normal. CA studies revealed significant coronary artery disease (CAD) in 51% (21 of 41 subjects). In those with CAD, 11 had reduced lactate extraction suggestive of ischemia. Nine of ten with xanthomas and 7 of 7 with abnormal exercise ECGs had CAD. Preclinical CHD (significant CAD and myocardial ischemia) occurs in the absence of LV functional abnormalities. The presence of xanthomas may be a useful predictor of advanced silent CAD in high risk males.

CORONARY HEMODYNAMICS AND METABOLISM IN PATIENTS WITH NORMAL CORONARY ARTERIES AND ANGINA PECTORIS.

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The basis for the occurrence of angina pectoris and myocardial ischemia in some patients with normal coronary arteriograms (NCA) remains obscure. To clarify the pathophysiology of this syndrome coronary sinus blood flow (CSBF), left ventricular hemodynamics oxygen consumption ($LV\dot{V}O_2$), and lactate extraction (XL) were measured at rest and during pacing induced angina pectoris in 11 patients with NCA, with ECG or metabolic evidence of myocardial ischemia and 10 patients with coronary artery disease (CAD). Differences occurred in CSBF rise with tachycardia at angina (NCA= 1.36±.18cc, CSBF ↑/beat vs CAD 0.85± .66cc, CSFF increase/beat, $p<.05$, as coronary resistance declined 40% in NCA and only 14% in the CAD patients, $p<.05$. These alterations during similar tachycardia stress (heart rate increased 81% in NCA and 73% in CAD), LV work (NCA = 5.5 ± .46 and CAD = 5.4 ± .43 Kg-m/min/m^2) and tension-time indices (NCA 3505 ±150 and CAD 3395 ± 204 mmHg-sec) were related to a marked increase, $p<.01$, in $LV\dot{V}O_2$ in the NCA patients (11.8 ± .08 →23.3±2.3ml/cc/min) compared to the CAD patients (12.4± 1.1 → to 15.8±1.6 ml/cc/min) during pacing. These data suggest that in some patients with NCA an inappropriate rise in LVO_2 usage (compared to patients with CAD) during tachycardia may exhaust available coronary blood supply and relate to the occurrence of angina pectoris and myocardial ischemia.

THE MICROSHOCK HAZARD: EXPERIMENTAL, ENVIRONMENTAL, AND EDUCATIONAL STUDIES

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An investigation of the endocardial ventricular fibrillation (VF) threshold for 6 newborn pigs and 40 adult dogs and epicardial threshold for 40 dogs and 4 humans having heart surgery was made. The environmental studies measured the leakage currents and ground characteristics of a cardiac operating room and intensive care unit, a coronary care unit and more than 106 patient rooms in 10 hospitals. Unique electrical designs were used in renovations of 4 cardiac and neurological facilities. An educational program was initiated for all nursing and new hospital personnel and courses and clinical training implemented in the Biomedical Engineering curricula. The results of the animal and human studies show that the VF threshold range is 200-300 microamperes for endocardial and 2-3 X greater for epicardial stimulation. The principles of the tree-structured grounding and isolated environments have been used in critical patient areas. These designs have been shown to be cost-effective, minimize electrical interference in monitoring, and eliminated the need for isolation transformers and other expensive devices. It is concluded that (1) present leakage current requirements for monitoring devices are sufficient, (2) the vast majority of the non-critical care areas studied meet or are better than present standards, (3) new simplified and inexpensive methods have been found and tested to provide better electrical safety for the critically ill patients, and (4) a low-key but continuous educational program for hospital personnel and interaction of engineers in clinical areas can achieve a high order of safety.

CONTRACTILE AND BIOCHEMICAL EFFECTS OF CORONARY REPERFUSION

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Immediate and delayed recovery of contractility upon reperfusion following progressively increasing periods of coronary occlusion extending from 30 mins. to five hours was studied in dogs and related to changes in high energy phosphate metabolism. Contractility was recorded by means of a strain gauge tipped catheter probe which measures myocardial fiber shortening. Release of coronary occlusion at any time up to 45 mins. was followed by prompt return of contractility along with complete recovery of adenosine triphosphate and creatine phosphate. With 1-2 hrs. of occlusion a delayed return of contractility occurred at 2 weeks after reperfusion; with 3 hrs. of occlusion recovery was only partial. Reperfusion after coronary occlusion of longer than 3 hrs. failed to restore contractility. Recovery of adenosine triphosphate synthesis (control = 5.45 μmoles/g) was 87%, 75% and 56% of control in experiments with release of coronary occlusion at one hr., two hrs. and three hrs. respectively. Corresponding values for creatine phosphate (control = 7.54 μmoles/g) were 95%, 83% and 60% of control. In conclusion, prompt recovery of contractility and high energy phosphate occurred with reperfusion after 45 mins. of coronary occlusion; with 1-3 hrs. of occlusion a delayed return of contractility and high energy phosphate occurred at 2 weeks after reperfusion. With occlusion of longer than 3 hrs., loss of contractility was irreversible.

RETROGRADE CONDUCTION IN WOLFF-PARKINSON-WHITE SYNDROME DEMONSTRATED BY HIS BUNDLE RECORDINGS AND VENTRICULAR PAIRED PACING.

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His Bundle Recordings (HBR) were performed in five patients with WPW complicated by frequent episodes of paroxysmal tachycardia (PT). The technique included 4 surface leads (I,II,III and V-1) recorded simultaneously with intracardiac leads: High right atrium (HRA), and His bipolar electrogram (HBE). An aditional HBE was often recorded by antecubital vein approach. Intermittent ventricular paired pacing at increasing rates and varying coupling intervals was performed in all pts. in order to determine the interval between the driving and testing stimuli (St-1 and St-2) at which reciprocation occurred. Various types of arrhythmias were observed. However, spontaneous and artificially-induced echoes and reciprocating tachycardias occurred in all pts. The onset and termination of the episodes could also be recorded in all cases. Reciprocal rhythms originated by ventricular paired pacing showed the following sequence : Ventricle (V) - low right atrial deflection (LRA) - HRA - His deflection- V , and the cycle started anew. The finding of a His deflection in the HBE after LRA, observed in all cases, demonstrates retrograde conduction through an accessory pathway (AP). Since reciprocal rhythms, rinduced by ventricular paired pacing, occurred at a critical St-1 to St-2 interval which ranged between 280 and 320 msecs., a difference of retrograde refractory periods between the AP and the normal A-V conducting system is suggested to explain the mechanism of reciprocating tachycardias.

EFFECTS OF VARIATIONS IN ARTERIAL pO_2 ON THE SEVERITY OF MYOCARDIAL ISCHEMIC INJURY FOLLOWING EXPERIMENTAL CORONARY OCCLUSION.

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Arterial oxygen tension is variable in patients with acute myocardial infarction. Hypoxemia in untreated and hyperoxemia in those receiving oxygen therapy are seen commonly. But the influence of variations in arterial pO_2 on the extent of myocardial damage following coronary occlusion is not known. Accordingly, in 28 open-chest dogs the left anterior coronary artery was occluded for 20 min repetitively while breathing room air, 10% O_2 and 40% O_2. Ten to 15 electrocardiographic epicardial leads were recorded in the distribution and vicinity of the site of occlusion. Average ST segment elevation ($\overline{ST}$) and number of sites showing ST segment elevation>2mV (NST), 15 min after occlusion, were used as indices of the severity and extent of ischemic injury. In 9 dogs during 2 occlusions with air breathing $\overline{ST}$ and NST did not change significantly (from 4.2±1.0 to 3.9±1.0mV and from 5.0±1.0 to 5.0±1.0 sites respectively). Ten percent O_2 lowered arterial pO_2 from 92±5 to 45±3mmHg, $\overline{ST}$ increased from 1.2±1.6 to 2.8±1.6mV($p<.01$) and NST from 2.2±2.8 to 6.5±2.6 sites ($p<.01$). Forty percent O_2 raised the pO_2 to 185±5mmHg, $\overline{ST}$ was reduced from 3.6±2.8 to 1.7±1.5mV($p<.01$) and NST fell from 5.3±3.1 to 2.7±2.7 sites ($p<.01$). Mean arterial pressure and heart rate showed no significant change throughout these experiments. It is concluded that following coronary occlusion hypoxemia is deleterious because it substantially increases myocardial damage and hyperoxemia is beneficial by limiting ischemic injury. These findings strongly suggest the danger of hypoxemia in patients with acute myocardial infarction and show the potential beneficial effects of oxygen therapy in reduction of myocardial damage.

UNSTABLE ANGINA: EXTENDED FOLLOWUP (1-4 YEARS) AFTER URGENT BYPASS OPERATION

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57 patients with intermittent chest pain at rest persisting more than 24 hours after hospitalization and accompanied by transient ischemic ECG changes had urgent saphenous vein aortocoronary bypass more than one year ago. Recent cases with shorter followup are excluded. 29 (49%) had previous infarctions (MI). 30 patients had a single graft, 25 had double grafts and 2 had triple grafts. There were 3 operative deaths (5%) and one sudden late death (2%) one year postop in an asymptomatic patient.

Followup extends from 12 to 48 mos. (mean 24 mos.). One patient is lost to followup. 33 survivors are Functional Class (FC) I, 12 are FC II and 7 are FC III. One patient had an MI immediately postop by Q wave criteria, and 3 had late MI - one following graft occlusion and 2 in areas not supplied by a graft. The single late death was presumptively attributed to an MI. 25 patients had angiography 3 to 28 mos. postop. 25/35 grafts were patent; only 3 patients had no patent grafts.

The extremely low mortality early and late postop (7%), the low incidence of MI (9%), and the excellent functional results after extended followup contrast strikingly with reports by others of results in similar high risk patients managed without urgent operations.

THE PROTECTIVE EFFECT OF PROPRANOLOL ON THE HYPERTROPHIED HEART DURING CARDIOPULMONARY BYPASS

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In an attempt to demonstrate the protective effect of Propranolol during anoxic cardiac arrest (ACA) for aortic valve replacement (AVR), 24 high risk patients were studied. All patients had severe calcific aortic stenosis with chronic congestive heart failure and left ventricular hypertrophy. AVR was done under moderate hypothermia (30°C) without coronary perfusion. All survived operative treatment. Twelve patients received intravenous Propranolol (0.5 mg.) just prior to aortic occlusion and were compared to the 12 non treated patients. Coronary sinus blood levels of calcium, phosphate, potassium, lactate and pyruvate were obtained prior to cardiopulmonary bypass, at the conclusion of ACA and at intervals following ACA. The Propranolol treated group had a significantly higher increase (mean 9.9 mg%) in coronary sinus blood phosphate when compared to the control (mean 3.2 mg%). The lactate/pyruvate ratio increased threefold in the Propranolol treated group (mean 79) when compared to the control (mean 24). Propranolol was used to treat 82 additional patients prior to ACA. Despite the severity of myocardial and aortic valve disease, none of these patients expired in the operative period. Ischemic contracture of the heart was abolished. Results of other parameters in the Propranolol pretreated patient demonstrated a protective effect on the hypertrophied myocardium during cardiopulmonary bypass.

THE ACCURACY OF VENTRICULAR VOLUME ANALYSIS BY QUANTITATIVE ECHOCARDIOGRAPHY IN PATIENTS WITH CORONARY ARTERY DISEASE WITH AND WITHOUT WALL MOTION ABNORMALITIES.

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Left ventricular (LV) end-diastolic (EDV) and end-systolic volumes (ESV) by quantitative echocardiography (QE) and angiocardiography (QA) were compared in 99 patients (pts) with coronary artery disease (CAD). LVVs by QE were derived using a cubed function of the measured LV internal dimension. In 34 pts with CAD unassociated with regional abnormally contracting segments (ACS), EDV and ESV by QE and QA correlated with r=0.939 and 0.930 respectively. In 65 pts with CAD+ACS, EDV and ESV by QE and QA correlated with r=0.922 and 0.795 respectively. The accuracy of EDV and ESV by QE was related to ACS location and, in 33 pts, to ACS extent (%ACS). Calculated EDV by QE and QA correlated significantly in pts with isolated anterior (A), inferior (I) or apical ACS and in pts with combined ACS with r-values >0.900. ESV by QE and QA correlated by only 0.714 in pts with AACS, 0.738 in pts with IACS and by 0.801 in pts with combined ACS. ESV by QE and QA correlated more significantly at 0.921 in pts with isolated apical ACS. Neither differences between LVEDVs, nor between LVESVs by QE and QA were statistically related to %ACS nor did there appear to be significant correlation (r=0.620) between differences in LV stroke volumes by QE and QA and calculated %ACS.

Quantitative echocardiography allows accurate quantitation of LVEDV over a wide range of LV sizes in pts with CAD. In the majority of pts with CAD+ACS, ESV by QE and QA did not correlate as significantly as did EDV suggesting that ESV by QE is affected by ACS in all pts save those with isolated apical ACS. The accuracy of ESV by QE thus appears related to ACS location but not to ACS extent.

OBSERVATIONS ON THE EFFECT OF OCCLUSION, NITROGLYCERIN AND PAPAVERINE ON CORONARY ARTERY BYPASS GRAFTS

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17 patients receiving 25 saphenous vein coronary artery bypass grafts have been studied at the time of surgery during the interval between the end of cardiopulmonary bypass and chest closure. Measurements have included aortic (AOP) and right atrial (RAP) pressures, left ventricular (LV) pressure measured by direct insertion of a catheter-tip manometer, heart rate and vein graft flow (VG flow) measured with an electromagnetic flowmeter. Following individual vein graft occlusions for 3 minutes there was no significant effect on AOP, RAP or LV dp/dt. LVEDP rose from 15 to 19mm Hg ($p<0.001$) and the relationship LV dp/dt max/LVEDP fell 152 to 135 sec^{-1} ($p<0.001$) indicating an adverse effect on LV function. HR rose from 88 to 91/min ($p<.05$). After release of the graft clamp the VG flow rose to 102ml/min from the resting value of 75ml/min ($p<0.01$) and fell to resting levels in 27 secs. Direct injection of nitroglycerin (NG), average dose 0.12mg, into the VG produced a rise in VG flow from 68 to 121ml/min lasting 66 secs ($p<0.01$). AOP, RAP and LV dp/dt fell significantly but there was no change in LVEDP or LV dp/dt max/LVEDP suggesting no alteration in LV function. Following direct injection of papaverine, average dose 7.6mg, into the VG, flow rose 70 to 149ml/min ($p<0.01$). The other changes observed were ECG T wave changes and a large rise in LV dp/dt min from -1120 to -750mm Hg sec^{-1} ($p<0.001$) suggesting interference with ventricular relaxation.

LEFT VENTRICULAR FUNCTION IN PATIENTS WITH NONTRANSMURAL MYOCARDIAL INFARCTION

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Patients with nontransmural myocardial infarction (NTMI) as diagnosed by ST-T wave changes on the electrocardiogram and elevation of serum enzymes are thought to have less left ventricular dysfunction and a better prognosis than those with transmural myocardial infarction (TMI) with Q waves. Myocardial performance was assessed in 11 patients with NTMI, 7 of whom were uncomplicated (Class I) and 4 of whom had evidence of mild to moderate congestive heart failure. (Class II); and in 25 with TMI, 14 in Class I, and 13 in Class II. The left ventricular filling pressure (LVFP) and cardiac index (CI) were measured with a Swan-Ganz thermodilution catheter. Left ventricular ejection fraction (LVEF), end diastolic volume (EDV), and percent of left ventricular wall akinesis were measured by gated cardiac blood pool scanning (GBPS) with I.V. technetium 99m albumin.

	NTMI	TMI
LVEF %	39±8	37±6
EDV ml	116±28	127±38
% Akinesis	24±13	30±11
LVFP mm Hg	14±5	16±8
CI liters/min/M^2	2.8±1	2.7±.6

There were no significant differences between the values in those with NTMI and TMI. LVEF and EDV in both groups were significantly different ($P<0.01$) from that obtained in 10 normal patients using GBPS 56±3% and 81±4 ml respectively. In conclusion this study suggests patients with NTMI have the same degree of myocardial dysfunction as TMI and does not support functional separation of patients on these electrocardiographic criteria.

INCREASED CARDIAC OUTPUT DURING INDUCED IRREGULAR RHYTHMS

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Irregular rhythm (IR) can increase cardiac output (CO), probably by potentiating contractility. Additional evidence for increased inotropic state during IR was obtained in 10 dogs. Aortic flow and left ventricular pressure were measured during regular rhythm (RR) and IR induced by simultaneous atrial and ventricular pacing from computer generated stimuli. IR patterns included 1) random sequences of cycle lengths with a flat distribution (RF), 2) ordered sequences alternating short and long cycles from the same flat distribution (ASL), and 3) sequences alternating maximum and minimum cycle lengths present in those patterns (AMM). Stimulus patterns had the same mean cycle length and the RF and ASL patterns contained equal numbers of any given cycle length. CO was higher with IR than with RR in all experiments. Compared to RR, increases in CO were 5% during RF rhythm, 15% during ASL rhythm and 25% during AMM. Since the cycle lengths in RF and ASL rhythms were identical, it is likely that differences in CO were due to differences in inotropic state. However, the Frank-Starling mechanism could not be totally excluded. Evidence that differences were due to varying inotropic state was obtained in 3 experiments in which pressures were recorded in a balloon in an isovolumic left ventricle preparation. Average peak pressures, maximum dP/dt and dP/dt at selected pressures were higher with IR than with RR and in most observations higher with ASL than with RF. Findings confirm that IR results in changed inotropic state, and show the maximizing of this effect by optimal sequencing of cycle lengths. A new method for study of rhythm effects on the cardiac state by controlling the sequence of a set of identical cycle lengths is reported.

MYOCARDIAL IMAGING WITH ^{99m}Tc MACROAGGREGATES. CLINICAL, HEMODYNAMIC, ECG, SURGICAL AND AUTOPSY CORRELATIONS

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Scintillation camera myocardial perfusion images were performed in 51 patients (pts) with proven or suspected ischemic disease. 1.5 mCi ^{99m}Tc macroaggregated albumin was injected directly into one or both coronary arteries.

Myocardial images were classified as normal (26) or abnormal (25) and the location of abnormality noted. 25 pts with abnormal images had myocardial infarction based on history (16/25), Q wave (19/25), or local contractile abnormality (22/25) singly or in combination. No pt with a normal image had a Q wave and only one of 25 had a local contractile abnormality. There was no correlation between an image defect and the presence of exercise induced ST depression. Ejection fraction was reduced ($p<.001$) in pts with abnormal images (43±14% vs. 61±11%). Pts with image defects (11) had transmural scar (10) or inferior hypokinesis (1) observed at surgery or autopsy; pts with normal images all had normal ventricles at surgery (4/4). A single pt with preinfarction angina without evidence of infarction had an image defect. Pts with less than 50% stenosis all had normal myocardial images (19 of 19). Pts with complete occlusions had corresponding image defects. Two pts with complete occlusions without infarctions had normal images. Six patients with stenoses of 75-99% had image defects; 5 had normal images.

We conclude that this technique identifies myocardial scarring secondary to infarction rather than areas of ischemia. Its sensitivity in the diagnosis of myocardial scar was better than the ECG or clinical history and comparable to the presence or absence of local contractile abnormalities on ventriculography. It appears useful in identifying scar and as a baseline for stress studies which may induce ischemia.

LONG TERM SURVIVAL FOLLOWING AORTIC VALVE REPLACEMENT

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Study is made of 77 long term survivors of aortic valve replacement. During follow up (24-98 mos, avg 50.2) angina was the leading cause of morbidity (21%) followed by symptoms of congestive heart failure (CHF) (19%). Complications consisted of peripheral emboli (8 pts), hepatitis (5 pts.), and endocarditis (3 pts.). Over one quarter of the patients had a persistent diastolic aortic murmur and 16% clinical evidence of hemolysis. Of the 7 deaths occurring in these patients over the follow up period, post mortem information was available in 6. These long term survivors (77) were compared to the group dying within 1 month of valve replacement (24) and those short term survivors (18) living less than 2 years. CHF was the most frequent preoperative disability and occurred with equal incidence in all 3 groups. Angina and syncope, however, were found with a statistically higher incidence in the short term survivors and hospital mortality groups, respectively. No statistical difference was found among the 3 groups in respect to patient age, functional class, hemodynamic lesion, duration of preoperative symptoms, left ventricular end diastolic pressure (LVEDP) or right ventricular systolic pressure (RVSP). There was, however, a significantly lower cardiac index (c.i.) of the hospital mortality group as compared with the 2 surviving groups. No significant correlation was noted between the duration of survival and the c.i., LVEDP, or RVSP. 59% of the patients were alive at the end of the follow up. Life table analysis showed marked drops at the end of 12 and 36 mos. It would appear that cardiac index is the best predictor of hospital mortality and that once a patient has survived 3 years, his chances for long term survival are excellent.

ENDOMYOCARDIAL DISEASE AND EOSINOPHILIA (LÖFFLER'S DISEASE): A Previously Rare Entity Which May Be Increasing In Frequency

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In a 40-year period Löffler studied at necropsy 2 patients with "fibroplastic parietal endocarditis with blood eosinophilia," an entity which now bears his name. During the past 10 years we have studied at necropsy 9 American patients (6 during the past 4 years) with this condition. Their ages ranged from 13 to 52 years; 8 were males. Five initially had been referred to the Cancer Institute with a diagnosis of eosinophilic leukemia and one had a positive Philadelphia chromosome. Eight patients had symptoms from 11 to 44 months (avg. 29) and one, for < 1 week. Except for the latter patient, all had extensive ventricular endomyocardial fibrosis with or without superimposed fibrin-platelet thrombi. The patient with symptoms for < 1 week had only endocardial thrombi, which were extensive, and she may represent a very early stage of this condition. The highest leukocyte counts in the 9 patients ranged from 79,000 to 150,000 per cu. mm, and the highest percentage of eosinophils on smear of blood, from 19 to 90%. All 9 patients died from congestive cardiac failure. The condition observed in our 9 patients is similar to the African condition, endomyocardial fibrosis. It is suggested that Löffler's fibroplastic parietal endocarditis, eosinophilic leukemia (without abnormal myelopoiesis), and endomyocardial disease of the African are the same disease at different stages of development.

THE ELECTROPHYSIOLOGIC BASIS FOR THE SUPPRESSION OF CARDIAC ARRHYTHMIAS BY VERAPAMIL

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Verapamil (V) is efficacious in the therapy of cardiac arrhythmias. Electrophysiologic studies have shown that V suppresses inward calcium (Ca) currents in cardiac and other excitable tissues. We used standard microelectrode techniques to determine the effects of V, 2×10^{-7} to 1×10^{-5} M on the electrophysiologic properties of isolated canine cardiac Purkinje fibers (PF). V<2×10^{-6}M had no effect on the PF action potential (AP). V=2×10^{-6}M enhanced phase 1 repolarization, bringing it to a more negative value, and increased the slope of phase 2. V≥6×10^{-6}M had more pronounced effects on repolarization and decreased AP amplitude, resting membrane potential, maximum rate of rise of phase 0, and membrane responsiveness. Changes in the effective refractory period were comparable to those in AP duration. Conduction velocity was slowed only by V≥6×10^{-6} M. V effects on phase 4 depolarization and automaticity induced by low potassium perfusates and/or ouabain (O), 2×10^{-7}M were studied as were O induced low amplitude potentials (LAP). V=2×10^{-6}M suppressed automaticity and LAP. V effects on the AP and LAP were partly reversible by increasing perfusate Ca concentration. These studies support the suggestion that V acts via mechanisms different from other antiarrhythmic drugs. Its effects on the AP plateau are consistent with blockade of an inward Ca current and suggest that V may suppress arrhythmias due to Ca induced slow potentials. Lower V concentrations do not alter phase 0 depolarization or conduction, but they do suppress automaticity and LAP's. The latter effects may also result from blockade of an inward current during diastole and are additional mechanisms whereby arrhythmias may be suppressed.

ARTERIAL ENDOTHELIAL AND SMOOTH MUSCLE CELLS: ARE THEY METABOLICALLY AND FUNCTIONALLY SIMILAR?

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Ultrastructural and histochemical studies have emphasized the unique characteristics of arterial endothelium as well as its differences in pharmacological responsiveness with smooth muscle cells from the same arterial segment.

We have recently carried out in vivo and in vitro studies on the functional and metabolic characteristics of such cells from large arteries. They suggest that known cytological dissimilarities may result from local environmental influences and occupational variations rather than from genetically coded, unyielding cell differences. The response of endothelial and smooth muscle cells from the same arterial segment to nanogram concentrations of several vasoactive agents, incorporation of colloidal electron markers and labeled homologous lipoprotein fractions was compared with similar cells obtained from large veins. While arterial cells showed similar responses, including significant increases in proliferative rates after short exposures to VLDL and LDL fractions, matching cell populations from the venous system resembled cardiac myocytes.

These studies suggest that endothelial and smooth muscle cells from large arteries may share a common ancestry. In the adult artery, they may represent specialized transitional stages of metabolically and functionally similar cell populations that may profoundly influence the development of vascular disease.

CONTROL OF THE TACHYARRHYTHMIAS ASSOCIATED WITH THE WOLFF-PARKINSON-WHITE BY AMIODARONE

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Amiodarone hydrochloride proved to be more effective than any of the drugs previously utilized for the prevention and treatment of the arrhythmias of the Wolff-Parkinson-White (WPW) syndrome. 11 patients with WPW and recurrent tachyarrhythmias were treated with oral doses between 300 and 600 mg daily. Paroxysmal supraventricular tachycardia in 6, atrial fibrillation in 4, and atrial flutter in 1, were the most significant arrhythmias. In most patients the arrhythmia caused a serious problem due to extremely rapid ventricular rate, frequency and duration of the episodes and ineffectiveness of other antiarrhythmic agents. In the 11 patients the arrhythmias were totally, easily and safely controlled during 2 to 8 months. The patients response was remarkably enthusiastic, in contrast with the less successful result of all preceding treatments. Tolerance was excellent. Amiodarone causes a significant prolongation of refractoriness in the normal (AV node and His-Purkinje system) as well as in the anomalous pathway, thus creating favorable conditions for prevention and interruption of any reentry mechanism requiring participation of both pathways.

INTERNAL MAMMARY ARTERY VERSUS AUTOGENOUS VEIN FOR CORONARY ARTERY BYPASS GRAFT

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A controversy exists concerning which vessel is best suited for coronary artery bypass surgery. This study deals with the morphologic alteration and susceptibility to atheromatous degeneration of the internal mammary artery graft (IMAG) as compared with the aortocoronary venous graft (ACVG). Six of 12 surviving dogs with IMAG's were fed a hyperlipidemic diet and 6 were placed on a regular diet. Three dogs in each group have been sacrificed 3-15 months post-surgery. Eight of 24 long-term surviving dogs with ACVG's were also on hyperlipidemic diets, and all were sacrificed 3-18 months post-surgery. Arteriography and electron microscopy were performed in selected cases, and histology was performed in all cases. All long-term IMAG's remained patent; 2 of 3 "regular" diet arteries were normal, with no intimal proliferation, while 2 of 3 "hyperlipidemic" IMAG's had atheroma and intimal proliferation. All ACVG's showed medial fibrosis and intimal fibrotic proliferation. In addition, 6 of 8 "hyperlipidemic" ACVG's had diffuse atheroma. Severity of arteriosclerotic involvement of the native coronary circulation was far less than that of the IMAG or ACVG. It may be concluded that: 1) In the normolipidemic condition, the IMAG undergoes significantly less severe histologic change than the ACVG, 2) Both the IMAG and the ACVG are susceptible to atheromatous degeneration, 3) Both types of grafts are apparently more prone to atheromatous change than the native coronary circulation. In these series, patency was not influenced by severity of histologic changes, and no grafts were occluded by virtue of the arteriosclerotic process.

PRINZMETAL'S VARIANT ANGINA: A PATHOPHYSIOLOGICAL AND CLINICAL KALEIDOSCOPE

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Fifteen patients with Prinzmetal's variant angina, defined as resting chest pain with ST elevation but without enzyme elevation, were studied clinically and by coronary angiography. Three groups were evident: 1) a stable form (1 patient), 2) unstable, accelerated angina (8 patients), and 3) a "post-infarctional" ischemic syndrome (with persistent anterior wall T inversion and intermittent ST elevation). All 3 patients treated medically from Group 3 expired within 6 weeks, while the 3 having surgery are well. Coronary angiography revealed negligible coronary disease in 4; single, double, or triple vessel focal disease in 10; and diffuse coronary atherosclerosis in 1. Coronary spasm was seen in 3. The onset or exacerbation of angina was temporally related to the initiation of sympatholytic antihypertensives in 2; to propranolol in 3; and all improved, at least transiently, after institution of nitrates; 1 after sympathomimetic vasodilators. Other manifestations of angina included fleeting ischemia - lasting seconds (2 patients), coexistent exertional pain in 9, and ischemia-induced ventricular tachycardia and/or fibrillation in 8. We conclude that Prinzmetal's variant angina represents a pathophysiological and clinical spectrum, at times amenable to medical therapy, and at other times presenting as malignant preinfarctional disease necessitating emergency bypass surgery.

NORMALIZATION OF THE ELECTROCARDIOGRAM DURING ANGINA PECTORIS IN PATIENTS WITH SUBENDOCARDIAL INFARCTION.

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Thirteen patients with ECG evidence of recent or old subendocardial infarction(SEI), defined as ST depression and T wave inversion in the precordial leads, have been observed to normalize their precordial ECG during angina pectoris(AP). By normalization, it is meant that the precordial ST segment returned to the isoelectric line and the T wave became upright. In 10 of these patients, the ECG normalized during spontaneous attacks of AP; in 3, the ECG normalized during AP produced by treadmill exercise(TME). Three of the 10 patients with SEI and spontaneous AP demonstrated reciprocal inferior lead ST depression in association with precordial ECG normalization. Coronary cineangiography in 6 patients(3 with spontaneous AP and 3 with TME AP)revealed total obstruction of the left anterior descending coronary artery(LAD) in each case. Two patients had single vessel disease(LAD); 4 had multiple vessel disease. Five of the 6 patients had a large area of akinesis or hypokinesis on left ventriculography. However, in 2 patients with precordial ST normalization and reciprocal inferior lead ST depression with spontaneous AP, there was no posterior left ventricular wall dysfunction or significant CAD in the vessels supplying this region. Of clinical significance in patients with SEI, the ECG during AP may either appear normal or falsely suggest acute inferior wall ischemia. With TME the ECG response may be normalization rather than further ST depression. Patients with SEI and ECG normalization with AP usually have extensive CAD with LAD occlusion and left ventricular dysfunction.

VALIDITY OF STRUCTURE IDENTIFICATION FOR MULTI-CRYSTAL ECHOCARDIOGRAPHY

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Phased, multiple crystal echocardiography is a major new advance in diagnostic ultrasound. Structure identification was verified in the present study in four cross sections: 1) long axis saggital of left and right ventricles (LV, RV), 2) coronal in the fourth intercostal space (ICS), 3) saggital along RV outflow tract, and 4) coronal of great vessel orientation in the second ICS. During hemodynamic study structure verification was achieved in nine patients by visualizing catheter echoes or indocyanine dye transit. Passage of dye through LA, LV and aorta was visualized in the saggital long axis and coronal (4 ICS) views. Right-sided structures were visualized clearly in patients with left-to-right shunts after left-sided dye injections. Right atrial echoes were observed behind the tricuspid valve in coronal section. Passage of dye through the right ventricular outflow tract and main pulmonary artery as well as visualization of catheter artifacts identified all landmarks in a precise fashion. Thus, this study supports the accuracy of real-time cross-sectional localization of all chambers and all valves in the positions used for cardiac imaging with multiple crystal echocardiographic systems. Because visualization of dye passage appears not unlike an angiogram, this system may find additional use in the catheterization laboratory in order to avoid excessive numbers of injections of contrast medium in patients with congenital heart disease.

CORONARY RISK PROFILE IN THE YOUNG ADULT POPULATION: THE MAJOR IMPORTANCE OF SERUM CHOLESTEROL. Antone F. Salel, MD; Dean T. Mason, MD, FACC; Carolyn K. Clifford, PhD; Andrew J. Clifford, PhD; Ashfaq Husain, PhD; Thomas Y. Cooper, MD.; Nemat O. Borhani, MD, FACC and Robert Zelis, MD, FACC. Univ. of Calif. School of Medicine, Davis, Ca.

Epidemiologic studies have established a strong relationship between serum cholesterol (CHOL) and premature coronary artery disease (CAD) in middle-age populations. In order to investigate the implications of this relationship in a young adult population, a total of 1456 entering UCD students (mean age 22 yrs) were screened. The screening included CHOL (true CHOL by the automated Levine-Zak method following isopropanol extraction) and a multiple risk factor (MRF) self-administered questionnaire. CHOL was correlated (simple, partial, multiple) with multiple risk factors (age, sex, obesity, smoking history, nutritional history, serum glucose, serum uric acid). Mean CHOL was 184 $\pm$ 40 mg/dl ($\pm$ SD) (mode 180, median 189). A striking proportion of the population had significantly elevated CHOL, 2.3% greater than 275 mg/dl, 5.9% over 250, 15.9% over 225 and 35% over 200. Significant correlates ($P<.01$) of serum cholesterol for males and females were obtained only in the populations of individuals with a family history of CAD. No significant correlation was observed with the other family histories such as diabetes and hypertension. Therefore, serum CHOL, an established risk factor of premature CAD in an older population is significantly elevated in a large percentage of this young adult population. In addition, a strong relationship between serum CHOL and a family history of CAD was detected. Since the yield for risk factor screening was so high, it seems prudent to direct major primary prevention efforts to this age group where the likelihood of finding minimal or reversible coronary vascular disease is high.

RESECTION OF LEFT VENTRICULAR ANEURYSM: REPORT OF 275 PATIENTS
Frank M. Sandiford, MD; George J. Reul, Jr., MD, FACC; John T. Dawson, MD; Don C. Wukasch, MD; Luigi Chiariello, MD; Grady L. Hallman, MD, FACC; Denton A. Cooley, MD, FACC.
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To evaluate the efficacy of combined aortocoronary bypass (ACB) with left ventricular aneurysm (LVA) resection, 275 patients (pts) who had LVA resection from 1958 to 1972 were reviewed and divided into 3 groups. Group I consisted of 102 pts who underwent LVA resection alone during the pre-ACB period from 1958 to 1969. From 1969 to 1972 there were 122 pts (Group II) who had LVA resection with ACB and 51 pts (Group III) who had LVA resection alone because of insignificant associated coronary artery disease (CAD) in other vessels. Multiple vessel CAD was present in 96% of Group II and in 77% of those pts in Group I who underwent selective arteriography. Preoperative congestive heart failure was present in 95% of Groups I and III and in 66% of Group II, while angina was present in 32% of Group I and in 90% of Group II. In Group I there was an early operative mortality of 17% as compared to Group II (12%) and Group III (10%). Follow-up data from 1 to 12 years demonstrated significantly higher late mortality in Group I. Factors affecting early and late survival in all groups included age, cardiac index, size of LVA, ejection fraction, coronary artery score and length of time after myocardial infarction. The anatomic location of the aneurysm in relation to the occluded and bypassed vessels and the estimated size of the left ventricle after resection have also been related to early and late mortality. Combined ACB with LVA resection significantly improved survival when compared to LVA resection alone.

THE CLINICAL SPECTRUM AND HEMODYNAMICS OF WOMEN WITH CHEST PAIN AND NORMAL CORONARY ARTERIES. Karen Sample, MD; H. Dominic Covvey; E. Douglas Wigle, MD; Allan G. Adelman,MD, Toronto General Hospital, Toronto, Canada.

Forty-nine women with chest pain and suspected ischemic heart disease were found to have normal coronary arteries by selective coronary angiography. Twenty-five had an alternative clinical or hemodynamic basis for chest pain: 10 had significant gastroesophageal disease; 2 had recurrent tachyarrhythmias; 5 had a prolapsed mitral valve leaflet on left ventricular angiography; 3 had cardiomyopathies with significantly elevated left ventricular end-diastolic pressures (mean (m) 24.7 mmHg); and 5 had hyperkinetic heart syndromes with high cardiac indices (CI)(m 5.59 L/min/m^2), increased ejection fractions (EF)(m 84.6%) and low arterial-venous oxygen (A-V O_2) differences (m 2.75 vol%).

Twenty of the remaining 24 patients (pts) had non-specific ST-T changes on their electrocardiogram. These pts had normal intracardiac pressures, CI's and A-V O_2 differences but, increased heart rates (HR)(m 92/min), prolonged corrected ejection times (ET)(m 426.1 msec) and decreased ejection rates (ER)(m 127.5 ml/sec/m^2). As a result the tension time index (TTI) was increased (m 1906.5 mmHg/sec/min), the diastolic pressure time index (DPTI) was reduced (m 2473.3 mmHg/sec/min) and the ratio of DPTI/TTI (an indication of the myocardial O_2 supply and demand relationship) was decreased (m 1.3). These pts also had small hearts with decreased end-diastolic (m 84.4 cc's), end-systolic (m 19 cc's), and stroke volumes (m 65.3 cc's) and high EF's (m 77.9%). The prolonged ET in the presence of an increased HR results in increased O_2 demand, diminished supply and may produce subendocardial ischemia and angina in these pts.

AORTIC VALVE REPLACEMENT WITH CONCOMITANT AORTOCORONARY BYPASS
Frank M. Sandiford, MD; George J. Reul, Jr., MD, FACC; Don C. Wukasch, MD; Luigi Chiariello, MD; Grady L. Hallman, MD, FACC; Denton A. Cooley, MD, FACC.
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One hundred consecutive cases of aortic valve replacement (AVR) with aortocoronary artery bypass (ACB) were reviewed to evaluate factors that influence early and late survival. Of these patients (pts), 65 had aortic stenosis (AS); 21 aortic insufficiency (AI); and 14 combined AS and AI. The majority (64%) were in Functional Class (FC) III and 44% were in FC IV. The predominant manifestations were angina and congestive heart failure (CHF) in 68%, angina alone in 17% and severe CHF alone in 15%. All pts had significant coronary artery disease. Of the 100 pts, 64 had single ACB; 33, double ACB; and 3, triple ACB performed simultaneously with AVR. Early surgical mortality was directly related to the FC IV status [15 deaths among 34 pts (23%)] and to the predominant presenting symptom of CHF alone [8 deaths among 15 pts (53%)]. In the group of pts in FC III who had combined symptoms of angina and CHF (43%), the early surgical mortality was only 7%. Long-term follow-up of the survivors from 1 to 4 years (mean 2.5 years) demonstrated that in 85% of the pts symptoms had disappeared or significantly decreased while in 8.5% symptoms remained unchanged or became worse. The late mortality of 6.4%, mainly due to progressive myocardial failure in FC IV pts, reflected a similar postoperative attrition of 2.5% per year observed in another group of 2273 pts who underwent ACB without concomitant procedures at this Institution. Despite the high operative risk in pts with advanced stages of coexisting aortic valve and CAD, the observed late survival rate appears to justify surgical therapy.

INCREASING HEMOLYSIS AND PREDICTABILITY OF ANEMIA IN THE CLOTH COVERED STARR-EDWARDS PROSTHETIC AORTIC VALVE
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This is an evaluation of the frequency and severity of increasing hemolysis in patients with hemolytic anemia from prosthetic valve replacement. In addition the serum lactic dehydrogenase (LDH) levels were evaluated in an effort to predict future anemia. Patients attended the postoperative clinic and had regular screening studies for hemolysis including serum LDH levels (normal 23-65). Patients were placed into anemic and non-anemic groups. LDH values for the anemic group include all yearly values for that patient including pre-anemia levels. The median LDH values for the groups are in the table and the numbers in parentheses are the patients studied that year.

Postop Year	1	2	3	4
Anemic	383 (16)	478 (19)	560 (12)	653 (11)
Non-anemic	181 (20)	150 (18)	187 (11)	147 (5)

The yearly increase in the anemic group is significantly different from the non-anemic group ($p < 0.005$). A subset of these patients showed a one-year increase of 3 LDH units in 15 non-anemic patients and 242 units in 17 anemic patients. The predictive value of the LDH level was assessed from values obtained prior to diagnosis. A value of 250 units predicted anemia on the next yearly visit with a 28% false positive and 4% false negative accuracy. The increasing hemolysis in the anemic patients may represent cloth wear (found in 5 of our 6 reoperated patients). Our current prevalence of anemia in the totally cloth covered aortic valve is 36/90 patients (40%). Therefore, monitoring of the LDH level is suggested. Values in excess of 250 units (4 times the upper limit of normal by other LDH methods) and/or increasing levels would suggest future anemia.

NON-TRAUMATIC DETERMINATION OF CARDIAC OUTPUT AND LEFT VENTRICULAR EJECTION FRACTION BY RADIONUCLIDE ANGIOGRAPHY.
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Previous reports indicated that cardiac output(CO)and left ventricular(LV)ejection fraction(EF)can be determined non-traumatically by radionuclide angiography(RCG). By recording the passage of a radioactive bolus through the heart a time-activity curve corresponding to LV volume changes can be derived.The purpose of the study was to develop a computer program for calculating CO and EF and to examine effects of background activity, scattered radiation and assignment of regions-of-interest(ROI)on these determinations. ^{99m}Tc human serum albumin was injected in 8 patients into the sup.vena cava during cardiac catheterization and the precordial activity recorded by an Anger camera interfaced with a small digital computer. Only that period of precordial activity, during which the bolus passage through the LV, was analyzed.After assigning LV and background ROI, EF was calculated automatically in time segments for the entire LV time-activity curve. The correlation coefficient between EF obtained from biplane cineangiograms (area-length-method) and EF calculated only during the early downslope of the LV time-activity curve and corrected for background activity was 0.92. EF was overestimated when the background ROI was too close to the LV and underestimated when the LV ROI encompassed other cardiac structures.There was good agreement between CO determined by RCG and dye-dilution($r=0.96$).It is concluded that although CO and EF can be measured by this non-hazardous technique with great accuracy,proper selection on the time-activity curve and proper assignment of the LV and background ROI are important.

MAIN LEFT CORONARY ARTERY DISEASE.
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In a 3 1/2 year period, 76 patients (pts) were found to have greater than 50% obstruction of the main left coronary artery (LCA) by coronary arteriography (CA). Clinical presentation was one of pre-infarction angina (PIA) in 30 pts (39%). Total occlusion of the LCA was found in two pts. Severe obstruction of other coronary vessels was present in most pts. Total occlusion was present in the right coronary artery in 32 pts (42%) and in the left anterior descending artery in 18 pts (24%). Isolated obstruction of the LCA was seen in four pts. Calcification of the LCA was seen fluoroscopically in 18 (24%). Intercoronary collaterols were visualized in 51 (67%). Of 70 pts undergoing left ventriculography, 49 (70%) had obvious contraction abnormalities. One pt (1%) became hypotensive and died at the termination of the procedure. Another pt developed myocardial infarction six hours after study and died within 24 hours. 66 pts (87%) were considered operable; 51 underwent surgery with an operative mortality rate (MR) of 12% and a total long term MR of 16%. 24 pts who survived CA were not revascularized; 6 (25%) eventually died. Of 30 pts with PIA, surgical MR was 13% (3 of 23), and nonsurgical MR was 57% (4 of 7) ($p<0.05$). It is concluded that LCA disease, especially when presenting as PIA, is a lethal condition which can be cautiously studied with an acceptable MR, and which usually can be treated surgically at an acceptable risk.

BUNDLE BRANCH BLOCK DUE TO HIS BUNDLE LESIONS
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We have previously reported that ischemic lesions in the His bundle (Hb) could result in bundle branch block patterns or even delta wave formation (Circulation,In Press). To more definitively study this problem, 10 in vivo and in vitro dog hearts were studied with extra- or intracellular recordings from the proximal and distal Hb as well as the right (Rb) and left (Lb) bundle branches (BB). Vagal slowing or atrial pacing showed normal intraventricular conduction within a wide range of heart rates, 20-300/min. Lesions were induced by ischemia (ligation of the anterior septal artery) or by trauma (needle puncture). In vivo,Hb damage was manifested as fragmented or split Hb potentials (H_1,H_2). Atrial pacing or proximal Hb pacing induced H_1-H_2 delay with concomitant Rb or Lb block. However, distal Hb pacing at comparable or even higher rates produced a normal QRS. In 3 dogs traumatic His lesions induced a split Hb potential which showed bradycardia-dependent right bundle branch block with concomitant delay and temporal alternation between H_1 and H_2. In vitro, using a modified Elizari preparation containing the Hb, proximal and distal Rb and Lb, normal conduction from Hb to proximal BB (10-15 msec) and Hb to earliest ventricular muscle activation (26-33 msec) was observed at pacing rates from 30-220/min. Resting potentials of Hb cells ranged from 65-85 mV. Punctate lesions placed above the branching Hb caused bradycardia-dependent (10-30 beats/min) delays to the distal Hb, 2:1 block as well as complete Rb or Lb block. In addition, some portions of the distal Hb were activated after the bundle branch potentials. We conclude that lesions in the Hb can cause bundle branch block probably due to dissociation of normally synchronous conducting pathways in the common bundle.

EFFECTS OF PROPRANOLOL ON HEMOGLOBIN-OXYGEN AFFINITY IN THE ANGINAL SYNDROME

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Propranolol alters red blood cell hemoglobin (Hb) affinity for oxygen (O_2) in vitro, shifting the oxyhemoglobin dissociation curve to the right, increasing the pO_2 at which Hb is 50% saturated (P50) and enhancing O_2 delivery to tissues. In vivo, a similar effect on Hb P50 has been demonstrated in normal subjects. The present study was designed to determine the effect of propranolol in patients (pts) with documented coronary artery disease (CAD) and the anginal syndrome.

While on daily propranolol ($\geq$ 40 mg.) for at least 6 months and after stopping propranolol for at least 10 days, the patients' Hb P50 was measured by the mixing technique (Edwards and Martin). In the three pts in whom propranolol levels were determined the mean concentration was 25.3 nanograms/ml ($\pm$ 11.7 SEM), generally considered within therapeutic range. All pts had $\geq$ 75% stenosis of one or more major coronary vessels, were non-smokers, had normal pO_2 at rest, and no evidence of hemoglobinopathy. Data in four pts were: Off Propranolol: Mean P50=25.3 mm.Hg. ($\pm$1.67 SEM); On Propranolol: Mean P50=29.1 mm.Hg. ($\pm$0.62 SEM); (p value <0.05). Each patient showed an increase in P50 on propranolol.

This demonstrated shift would increase O_2 delivery 20-30% to marginally perfused myocardium. In addition, decreased Hb-O_2 affinity could maintain systemic oxygen delivery while sparing myocardial work. Thus propranolol, in addition to its negative chronotropic effects, may increase myocardial tissue oxygen delivery in pts with anginal syndrome.

DEEP VENOUS THROMBOSIS AS A DIAGNOSTIC CLUE TO PULMONARY EMBOLISM.

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Current techniques of diagnosing pulmonary embolism (PE) are either non-specific (e.g. lung scanning) or invasive (e.g. pulmonary angiography). Since the majority of pulmonary emboli originate in the legs, identification of deep vein thrombosis (DVT) may serve as a clue to coexistent PE.

Fifty-eight patients who were suspected to have PE on clinical grounds underwent electrical impedance plethysmography (IPG) and pulmonary angiography for diagnosing DVT and PE respectively. Of these, 36 had PE and 38 had DVT. Close association (95%) between the two diseases was seen, as shown below:

PTS		With DVT		Without DVT	
With PE	(36)	34	(95%)	2	(5%)
Without PE	(22)	4	(18%)	18	(82%)

Further analysis indicated that in these patients, diagnosis of DVT established the diagnosis of PE in 90%, whereas patency of the veins excluded the possibility of PE in an equal percentage, as shown below:

PTS		With PE		Without PE	
With DVT	(38)	34	(90%)	4	(10%)
Without DVT	(20)	2	(10%)	18	(90%)

It may be inferred from the above that in patients with cardiopulmonary findings suggestive of PE, recognition of DVT points to coexistent PE in 90%. It may also be stated that in a patient with suspected PE, if the deep veins are patent by IPG, the probability that the patient does not have PE is 90%. Thus, in view of its simplicity and specificity IPG may prove to be a valuable screening procedure in the diagnosis and management of venous thromboembolism.

A NEW POSITIVE INOTROPIC DRUG, RO2-2985/1 (X537A) WITH POTENTIAL USE IN THE TREATMENT OF CARDIAC DISEASE.

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An antibiotic ionophore, RO2-2985/1 releases calcium (Ca) from sarcoplasmic reticulum (SR), inhibits Na^+,K^+-ATPase and produces positive inotropism. Parameters measured in anesthetized dogs before and after right atrial or femoral vein injections of RO2-2985/1 (0.25-1.0 mg/kg) (Paired "t" test) were:

	N	Avg. of Controls	Avg. of Max. Values after RO2-2985/1	"p"
Mean blood pressure	17	104	141 mm Hg.	<.01
Heart rate	16	150	178 beats/m.	<.01
Aortic blood flow	11	1.9	3.2 L/min.	<.01
Vascular resistance	11	59	67 "R" units	NS
L.Circumflex flow	9	100	228 ml/min.	<.01
L. Ventricular force	17	100	168%	<.01
R. Ventricular force	17	100	189%	<.01
L. Ventricular dF/dt	17	100	204%	<.01
R. Ventricular dF/dt	17	100	214%	<.01

Doses up to 5 mg/kg caused no arrhythmias or alteration in response to isoproterenol (ISO), epinephrine (E) or norepinephrine (NE). Similar responses were noted in normal and shock. Effects were sustained in animals up to 9 hrs.; tyramine, NE, E or ISO at this time resulted in normal effects. Awake, chronically instrumented dogs responded similarly. β-blocked dogs also showed marked response to RO drug. Suggested mechanism of action: Very slow release of some neurotransmitter, secondary to a Ca^{++}-H^+ exchange. These findings of prolonged increased blood pressure, coronary and aortic flow and dF/dt have potential importance in the treatment of certain types of heart disease.

PHYSIOLOGICAL LIMITATIONS OF INTERNAL MAMMARY ARTERY AS CORONARY BYPASS

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Because of its higher patency rate, internal mammary artery-coronary artery (IMA-CA) anastomosis has recently found favor in the revascularization procedures of the myocardium. Nevertheless, it is important to establish that internal mammary artery provides for the myocardial demands for revascularization notwithstanding the many other advantages it offers. Two-hundred fifty-two IMA-CA anastomoses were performed through December, 1972. Postoperative selective coronary arteriography, left ventricular (LV) angiography and necropsy findings in patients followed from 3 weeks to 2 years were correlated with preoperative distribution of coronary artery disease LV angiography and blood flows determined intra-operatively. Lower mammary blood flows were recorded in those who died or developed angiographic occlusions. Although the use of IMA is justified if considering patency rates only, its physiologic limitations in terms of flows need to be recognized. Mean flows were substantially lower if relatively long and narrow vessel was used as well as when preoperative LVEDP was elevated. The IMA provides lower blood flows than vein grafts and when mammary flow is below a critical level, the rate of angiographic narrowing is high. Simultaneous successful vein grafts have been found to compensate for this decreased mammary flow and the postoperative ventricular status depended more on the vein grafts. When vein grafts had narrowed postoperatively, LV supplied by mammary had deteriorated despite mammary-coronary anastomosis being patent. Criteria for its use in the individual patient and its place in myocardial revascularization is assessed.

PRESERVATION OF CARDIAC CELLULAR INTEGRITY BY METHYLPREDNISOLONE IN ACUTE MYOCARDIAL ISCHEMIA. James A. Spath.Jr., Ph.D., David L. Lane, B. A. and Allan M. Lefer, Ph.D. Univ. of Va. Sch. of Medicine, Charlottesville, Virginia

Methylprednisolone (MP) 30 mg/kg, or its vehicle was administered intravenously to cats subjected to acute myocardial ischemia(MI) by occlusion of the left coronary artery. Experimental groups included: sham MI + MP, MI + vehicle, MI + MP at 30 minutes pre-occlusion, and MI + MP at 60 minutes post-occlusion. MP induced no significant hemodynamic effects. Coronary artery occlusion resulted in a significant decrease in heart rate and arterial blood pressure as well as a significant elevation of the S-T segment of the ECG. Pre- or post-treatment of cats with MP resulted in a decline in S-T segment to control values within 4-5 hours,while the S-T segment of diluent-treated cats remained elevated. Moreover, creatine phosphokinase (CPK), cathepsin D and β-glucuronidase activities were reduced 43%, 41% and 33% respectively in ischemic myocardium when compared with non-ischemic regions. In contrast, pre- or post-treatment of cats with MP prevented the activities of the lysosomal hydrolases of β-glucuronidase, cathepsin D and CPK from decreasing in ischemic cardiac tissue five hours after occlusion. Furthermore, plasma CPK activity increased 8-fold in diluent-treated cats following occlusion, but pre- or post-treatment of cats with MP limited the increase in plasma CPK activities to values not significantly different from that of sham-operated cats. These data indicate that methylprednisolone prevents the release of CPK and lysosomal hydrolases from ischemic myocardium. Thus, glucocorticoid stabilization of lysosomal and cellular membranes limits the spread of injury of cardiac tissue which is mediated by release of lysosomal acid hydrolases following infarction. (Supported by a grant from NHLI.).

GLUCOSE-INSULIN-POTASSIUM, PATIENT SURVIVAL, AND THE ACUTE MYOCARDIAL INFARCTION
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Twenty-five patients (pts) with symptoms of acute myocardial infarction (AMI) less than 12 hrs in duration were selected for a continuous infusion of glucose-insulin-potassium (GIK). Ten pts received 225 mg glucose (G)/min or 1.5 ml/min of a solution containing 15 g G, 25 U regular insulin (RI), 40 mEq potassium chloride (KCL)/L, and 15 pts received 500 mg G/min or 1.7 ml/min of a solution containing 30 g G, 50 U RI, 80 mEq KCL/L into the right atrium for 48 hrs. Time lapse from original pain to initial infusion ranged from three to 12 hrs. Serial pulmonary artery end-diastolic pressure (PAEDP), cardiac index (CI) and EKG were recorded. G and free fatty acids (FFA) were measured every four hrs. Electrolytes, osmolality, and enzymes were measured every 12 hrs. Additional therapy (lidocaine, procaine amide, quinidine, furosemide) was used if necessary. Many of these pts were considered at high risk (S_3 gallop, 13/25; PAEDP >20, 11/25; precordial bulge, 9/25; cardiomegaly by x-ray, 7/25; pulmonary edema by x-ray, 8/25; cardiac arrest, 7/25; complete heart block, 3/25; plasma FFA >1.2 mEq/L, 11/25. Despite expected mortality from above findings, 23/25 (92%) pts survived the acute episode and were discharged from the hospital. One pt with four hours of cardiogenic shock died two hrs after GIK was begun. Autopsy revealed a left main coronary stenosis. A second pt with a large anterior infarction and previously documented severe three vessel disease with diffuse ventricular akinesis died after 18 hrs of GIK infusion. CONCLUSION: These data from certain high risk pts with AMI suggest that a continuous infusion of GIK may contribute to pt survival.

TWO ANOMALOUS ATRIOVENTRICULAR CONNECTIONS IN PATIENTS WITH THE WOLFF PARKINSON WHITE SYNDROME.
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2 patients with Type B WPW and 1 patient with Type A WPW have been studied using intracardiac recordings and programmed electrical stimulation of the heart.In patient 1.atrial premature beats showed a Type B WPW electrocardiographic pattern. At an atrial premature beat interval of 350 msec this changed to a Type A WPW pattern and at an atrial premature beat interval of 230 msec supraventricular tachycardia was initiated.During tachycardia retrograde left atrial activation occurred 65 msec before right,suggesting that the bypass functioning retrogradely during tachycardia was on the left side of the heart as occurs in Type A WPW. Similar findings were obtained in Patient 2. Both patients therefore have a right sided AV bypass which is used antegradely during sinus rhythm. During tachycardia this bypass is not used but a left sided bypass functions. Patient 3 had Type A WPW and during tachycardia retrograde left atrial activation occurred 40 msec before right,consistent with a left sided bypass. However during premature atrial stimulation with antegrade conduction solely in the His pathway the A-H time did not prolong and the H-V time was short at 15 msec. Ajmaline administration led to normal prolongation of the A-H time with atrial premature beats and the H-V time became 30 msec. These findings suggest the presence of an AV nodal bypass inserting low in the bundle of His in addition to the left sided Kent bypass. The former bypass appeared not to be used during tachycardia. These findings emphasize the importance of an electrophysiological study in patients with the WPW syndrome considered for surgery for their dysrrhythmia. If only surface electrocardiograms are relied upon the wrong bypass may be cut at surgery.

POSTOPERATIVE HEMODYNAMIC AND ELECTROPHYSIOLOGIC EVALUATION OF THE MUSTARD PROCEDURE
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Cardiac catheterization, including venous, retrograde and His bundle studies, has been accomplished 1 to 4 years postoperatively in 6 of 14 children in whom the Mustard procedure was performed in infancy or early childhood for transposition of the great arteries. The His bundle potential was recorded in the new right atrium near the mitral valve. P_{50} was normal in all children. Right to left shunting at the SVC-baffle junction, present in 3 children, was minimal in 2, 36% of the cardiac output in the third. An atrial hydrogen positive left to right shunt was present in 1 child. SVC obstruction was clinically manifest in 1 child and an SVC-RA mean pressure gradient ranging from 6 to 12 mm Hg was present in 3. Subvalvular pulmonic stenosis, present in 3 children, had decreased from preoperatively in 1, had increased in 1, and remained unchanged in 1. Pulmonary vascular resistance was normal in all children. Left ventricle ejection fraction was .4 to .6. Right ventricular end-diastolic pressure ranged from 4 to 17 mm Hg before angiography and after angiography ranged from 12 to 20 mm Hg. Though all children have experienced atrial dysrhythmias, none were present during His bundle recording. All intracardiac intervals were normal at rest. Conduction was intact with pacing rates up to 170. Sinus node recovery time was also normal. These findings indicate intactness of the AV node-His bundle-Purkinje system, despite the occurrence of atrial dysrhythmias. Though most children are clinically well, hemodynamic abnormalities may be present.

AN ENERGY DOSE FOR HUMAN VENTRICULAR DEFIBRILLATION

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An electrical dose for trans-chest electrical ventricular defibrillation has been reported in animal subjects, but not in humans. In this study trans-chest ventricular defibrillation attempts in 111 human subjects were reviewed to determine the relationship between body weight and electrical countershock strength required for success. The percentage of successful defibrillations decreased progressively as body weight increased in the following way: 100 % success for patients weighing less than 50 kg; 75 % for 50 to 59 kg; 70 % for 60 to 69 kg; 82 % for 70 to 79 kg; 63 % for 80 to 89 kg; 40 % for 90 to 99 kg; and 0 % for greater than 99 kg. Decreasing success within the 50 to 90 kg range and complete failure to defibrillate patients heavier than 90 kg indicates that most commercial defibrillators have inadequate output for use on adult humans. The threshold dose required for defibrillation was establishes for 11 subjects. The dose relationship of average threshold energy and body weight is expressed by the relationship $U = 1.88\ W^{1.15}$, where U is energy (watt-seconds) and W is body weight (kilograms). Suggested guidelines for dosage in humans are 3.5 to 6.5 watt-seconds delivered energy per kg body weight up to 50 kg and the maximum energy output of the defibrillator (or 400 watt-seconds in most commercial units) for greater than 50 kg of body weight.

AGE-RELATED CHANGES IN SENSITIVITY TO DIGOXIN

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Clinical studies indicate that infants are less sensitive to digitalis than adults. In order to study the mechanism by which age alters sensitivity to digoxin (D), 1 month old puppies (P) and adult (A) mongrel dogs were anesthetized. Half the dogs in each group were then given H^3-D intravenously at a rate of 2.5 µg/kg/min until ventricular tachycardia (VT) occurred. The other half served as controls. At VT, the animals were sacrificed and left ventricular myocardium analyzed for D and (Na^+,K^+)-ATPase activity. Time to VT was 96.3 ± 4.3 min in P and 58.2 ± 2.2 min in A ($p < 0.01$). (Na^+,K^+)-ATPase activity was 13.1 ± 1.9 in P and 11.4 ± 0.5 µM Pi/mg protein/hr in A not given D (p=NS). At toxicity (Na^+,K^+)ATPase was inhibited 56.5 ± 5.8% in P and 55.2 ± 4.1% in A (p= NS). Myocardial D was 828.2 ± 40.5 ng/gm in P and 503 ± 25.4 ng/gm in A ($p<0.01$). Microsomal-bound D was higher in P than A, 60.3 ± 3.3 vs. 32.0 ± 2.5 ng D/mg protein ($p<0.01$), while plasma D at toxicity and microsomal protein yield were similar in animals given D. These studies suggest that (Na^+,K^+)-ATPase inhibition at toxicity is similar in P and A, but that (Na^+,K^+)-ATPase is less sensitive to D in P than it is in A.

PARALLELISM BETWEEN CYCLIC AMP-DEPENDENT PROTEIN KINASE-CATALYZED PHOSPHOLAMBAN PHOSPHORYLATION AND STIMULATION OF CA-TRANSPORT IN CARDIAC SARCOPLASMIC RETICULUM

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We have recently shown that bovine cardiac cyclic AMP-dependent protein kinase (PK) stimulates both Ca-uptake and Ca^{2+}-activated ATPase of dog cardiac microsomes enriched in sarcoplasmic reticulum (SR). Enhanced Ca-transport is associated with phosphorylation of phospholamban, a 22,000 dalton protein in which the γ-P of ATP is incorporated as phosphoserine. To demonstrate a causal relationship between phospholamban phosphorylation and Ca-transport stimulation, cardiac SR (0.5 mg/ml) was incubated at 25° C for 10 min. in 40 mM histidine (pH 6.8), 120 mM KCl with and without 1 µM cyclic AMP and 0.01-2.0 mg/ml cardiac PK in the presence of 5 mM MgATP containing [γ-^{32}P] (Reaction A) or no label (Reaction B). Reaction A was stopped by 10% TCA, and hydroxylamine-stable phosphoprotein was determined. Aliquots of Reaction B were added to $^{45}CaCl_2$ + oxalate for Ca-uptake measurement. When PK concentration was varied, phospholamban phosphorylation was closely correlated with increased Ca-uptake. Saturating cardiac PK concentrations (>0.5 mg/ml) caused approx. 4-fold increases in both. Furthermore, the curve relating phospholamban phosphorylation to Ca-uptake stimulation by rabbit skeletal muscle PK was virtually identical to that obtained with bovine cardiac PK. (For combined data N=21, r=0.96, p<0.001). Enhanced Ca-transport thus correlates highly with phosphoprotein formation, providing further evidence that protein kinase-catalyzed phospholamban phosphorylation stimulates Ca-transport by cardiac SR.

Supported by NYHA, NIH Grants HL-13191 and HL-15764, and Contract NIH-NHLI-72-2973-M.

ACTION POTENTIALS AND ELECTROGRAMS PRECEDING VENTRICULAR FIBRILLATION DURING ACUTE MYOCARDIAL INFARCTION

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The presence of distinctive electrophysiologic changes anticipating ventricular fibrillation (VF) following myocardial infarction was explored by means of suction electrode recordings of monophasic action potentials (MAP's) and epicardial electrocardiography. After obtaining control records in 20 dogs anesthetized with pentobarbital, the left anterior descending coronary artery was externally occluded for 10 minutes. Two types of changes in MAP's and electrograms occurred in infarcted zones. The first response, Type A, anticipated development of localized VF within the infarct, the MAP's were characterized by increased amplitude and disappearance of the plateau. Morphology of the MAP's acquired a sinusoidal appearance with deep negative troughs. The electrograms consisted of tall bizarre R waves with smooth downstrokes and intermittent negative after-potentials. Type A changes occurred in 7 of 9 dogs. Of the 2 remaining dogs, 1 exhibited ventricular tachycardia and the other had leakage of the balloon occluder which lead to normalization of Type A changes. The second response, Type B, had a lesser predisposition to VF occurring in 2 of 11 dogs. The MAP's were characterized by a temporal decrease in amplitude and maximal rate of depolarization. Duration of MAP's responded in a biphasic manner, first increasing due to development of a "hump" or prolongation of terminal phase three repolarization and then progressively decreasing. Type B electrograms exhibited increased amplitude of R complexes with elevated ST segments and upright T waves. The present study provides a distinctive electrophysiologic marker which antedates VF.

LOCAL MYOCARDIAL FUNCTION DURING ACUTE CORONARY OCCLUSION IN THE CONSCIOUS DOG

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Local, segmental function of the myocardium was characterized in 9 awake, healthy dogs before and during acute coronary occlusion (CO). The dogs were instrumented with a micromanometer, a hydraulic cuff around the origin of the left circumflex artery, and 3 pairs of 2mm ultrasonic crystals. These were implanted 1cm apart near the endocardium in an ischemic segment (IS), a distant control segment (CS), and a marginally ischemic segment (MS) as determined by epicardial ECG mapping at surgery. End-diastolic length (EDL) and extent of shortening (ΔL) were measured; instantaneous power was derived by analog computations as segment velocity x LV pressure; external segmental work was obtained by integration. During CO heart rate increased from 78 to 105 ($p<.001$). In IS, CO resulted within a few beats in decreased ΔL and appearance of a late systolic bulge, followed within 1 min by a holosystolic expansion; EDL increased by 0.6mm (6%, $p<.01$) and stroke work decreased by 768 gm-cm (-90%, $p<.001$) implying passive deformation. In MS, EDL increased by 0.4mm ($p<.01$) while ΔL decreased by 0.8mm (-50%) and stroke work decreased 295 gm-cm (-45%) ($p<.01$). In CS, an initial increase in ΔL occurred at constant EDL; subsequently EDL increased by .34mm ($p<.001$), and ΔL increased by 0.26mm (15%, $p<.01$); the latter increase was linearly related to the increase in EDL ($r=.94$) indicating use of the Frank-Starling mechanism in the CS. These findings characterize local segmental responses of the left ventricle to acute CO, and provide a practical and sensitive approach to quantification of functional effects of coronary occlusion in the awake animal.

EVIDENCE FOR SEVERAL LEVELS OF BLOCK WITHIN THE AV NODE, FOLLOWING PREMATURE ATRIAL STIMULI, AS SHOWN BY MULTIPLE MICROELECTRODE RECORDING IN THE ISOLATED RABBIT HEART.

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In order to define the site and mechanism of atrioventricular (AV) block, the pattern of AV nodal activation was mapped in isolated rabbit hearts, following premature atrial stimulation, by multiple intracellular recording, using a 10 microelectrode "brush". After every 10 th basic beat, the atrium was prematurely stimulated after three different intervals. All three premature impulses were concealed within the AV node. The premature beat with the longest preceding cycle traversed nearly the whole AV node, before being blocked close to the beginning of the His bundle. On shortening the interval, the impulse was blocked in the middle of the node, while the earliest premature beat was blocked close to the atrial margin of the node. In all instances, a large area in which action potentials showed an increasingly lower amplitude and rate of rise was interposed between the area of normal action potentials and the area of no response. This area of gradually decreasing responses was smallest for the late premature beat, and largest for the earliest premature beat. Our results show that depending on the coupling interval of the premature beat, block may occur at severals levels of the node, and that the zone of block is typically accompanied by a zone of decremental conduction.

ANGIOTENSIN IN THE TREATMENT OF HYPOXIA IN PATIENTS WITH TETRALOGY OF FALLOT

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Prompt therapy of hypoxic spells in patients with Tetralogy of Fallot (TOF) is frequently lifesaving. With the improvement in surgical management, especially correction of TOF in infants and small children, good medical treatment while preparations for surgery are underway is mandatory. However, medical management remains less than optimal. In a search for a more useful form of medical management we have administered angiotensin to eleven patients with TOF with varying degrees of systemic arterial desaturation to assess its hemodynamic effects. After completing routine cardiac catheterization and establishing the diagnosis of Tetralogy of Fallot, baseline systemic arterial saturations were obtained. Angiotensin (Hypertensin, Ciba Pharmaceutical Co, N.J.) was administered through the venous catheter at a rate of 0.2-0.5 microgram/kg/min to raise the systemic systolic pressure 20-40 mm Hg above the baseline pressure. Systemic arterial saturation was significantly increased in all patients. The percentage increase varied from 8% to 124% and averaged 36%. Four patients with protracted spells and very ill despite the usual methods of treatment (O_2 by mask, parenteral morphine) responded dramatically and were maintained on intermittent or sustained angiotensin administration until surgery could be performed. Our experience shows that angiotensin should be tried in the emergency treatment of patients with acute hypoxic spells who fail to respond to the generally accepted methods of treatment.

HIS BUNDLE RECORDINGS IN CORRECTED TRANSPOSITION OF THE GREAT VESSELS.

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His bundle electrograms (HBE) were recorded in five patients with corrected transposition of the great vessels. In the four patients with normal sinus rhythm and normal P-R interval, the HBE showed functional changes of atrioventricular conduction: (1) increase in the A-H interval in two cases; (2) increase in the H-V interval in one case, more evident during a spontaneous episode of A-V block of the Mobitz I type; (3) increase in the internodal conduction time, namely between the sino-atrial and atrioventricular nodes (P-A interval) during atrial stimulation in the fourth case; and (4) the fifth patient had complete A-V block, the block was post-Hisian with conduction disturbance at the level of the His bundle, related to changes in the morphology and duration of the H spike.

The conduction disturbances observed in the region of the A-V node and in the His bundle and its branches can be explained by the histopathological changes described in cases of corrected transposition of the great vessels.

EFFECTS OF INOTROPIC INTERVENTIONS ON THE NORMAL AND ISCHEMIC MYOCARDIUM IN CONSCIOUS DOGS. Stephen Vatner, M.D., Robert McRitchie, M.B., Peter Maroko, M.D., Thomas Patrick and Eugene Braunwald, M.D., FACC. Dept. of Med., Harvard Med. Sch., & Peter Bent Brigham Hosp., Boston, Ma.

While cardioactive sympathomimetic amines and exercise improve function in the normal heart, their action on the ischemic myocardium is not clear. 9 conscious dogs were studied 2-4 weeks after implantation of endocardial left ventricular(LV) diameter(D) gauges for LVD and dD/dt, i.e. velocity, miniature LV pressure(P) gauges for LVP, dP/dt and dP/dt/P, arterial(A) P catheters, Doppler L circumflex coronary(C) flow(F) probes, and occluders on L main C artery. In normal dogs isoproterenol(ISO), .4ug/kg/min, decreased mean AP (-15mmHg), LV end diastolic(ED) D (-2.8mm), and increased CF from 38 to 96ml/min, dP/dt/P from 60 to 133sec^{-1} and heart rate(HR) from 73 to 167B/min. Mild exercise(EXC) doubled CF, dP/dt/P and HR without changing AP or LVEDD significantly. Dobutamine(DOB), 40ug/kg/min, a cardiospecific β adrenergic agonist with minimal chronotropic and peripheral vascular activity, increased CF (+20 ml/min) and dP/dt/P (+72sec^{-1}) without changing LVEDD, AP or HR. Norepinephrine(NE), .8ug/kg/min, increased mean AP (+48mmHg), CF (+12ml/min), dP/dt/P (+59sec^{-1}) without changing LVEDD or HR. Partially occluding the C artery to reduce CF from 38 to 26ml/min induced marginally impaired LV function as reflected in a fall in dP/dt/P (-5sec^{-1}) and a rise in LVEDD (+1.3mm). Then, ISO and EXC produced paradoxical responses, dP/dt/P falling by 33 and 36sec^{-1} and LVEDD rising 1.1 and 2.2mm respectively. NE still improved LV function, dP/dt/P rose (+33sec^{-1}) and DOB produced an intermediate response changing dP/dt/P only slightly. Thus, inotropic interventions (ISO,EXC) that increase HR and contractility without increasing AP can elicit paradoxical deleterious responses in global myocardial ischemia, while NE, which increases contractility and C perfusion, improves function in the ischemic as well as the normal myocardium.

AORTOCORONARY BYPASS IN THE DIABETIC PATIENT
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The hospital records of 112 consecutive elective aortocoronary bypass grafts were reviewed to evaluate the effect of diabetes mellitus (DM) on operative results. Excluded were associated left ventricular aneurysm resection, valve replacement, or emergency procedures. 35 patients (31%) had DM (8 of these newly discovered during workup for angina). Preoperatively the DM and non-diabetic (NDM) patients were of similar average age and sex, had similar incidence of hypertension, smoking, family history of coronary disease, and number and distribution of vessels involved. The DM group (NDM in parentheses) had a greater frequency of prior MIs 63% (NDM 45%), preinfarction angina 20% (3%), dyskinetic left ventricles 49% (40%), LVH 54% (42%), obesity 63% (44%), CHF 15% (9%), mitral insufficiency 14% (6%), and a greater number of Class IV patients 23% (7%). Intraoperatively, DM patients received more triple grafts 26% (17%). Duration of bypass was the same in both groups. Average flow rates of grafts were similar: RCA 74 cc/min (72), LAD 67 (60), circumflex 61 (55). Operative mortality: 4 DM - 11% (3 NDM - 4%). One late death occurred in each group. Postoperatively, the DM group had more serious complications: CVA 6% (0); increased blood loss 11% (4%); wound infections 9% (3%); sternal separations requiring reoperation 6% (NDM - 1 flail chest, no reop); elevated BUN 20% (10%), one DM required peritoneal dialysis; longer postop hospitalization 16 days (13); DM patients had fewer post-surgical myocardial infarctions 6% (12%). Patients with DM can be selected for aortocoronary bypass using the same criteria as NDM. Our flow rates in grafts were similar, placing doubt on the significance of small vessel involvement in the myocardium. New DM was found in 7% of our patients.

ANALYSIS OF VULNERABILITY CHANGES DURING ACUTE CORONARY OCCLUSION AND RELEASE
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Antiarrhythmic drugs affect differently ventricular fibrillation (VF) arising from coronary occlusion (CO) and from release (R) of the obstructed vessel. The basis for this disparity of drug action is undefined. The present study examined the mechanism accounting for the differences in ventricular vulnerability during CO and R. A balloon catheter was placed around the left anterior descending coronary artery 7 days prior to definitive study. Under pentobarbital anesthesia VF threshold (VFT) was determined by the technique of sequential R/T pulsing. Four periods of 10 minute CO followed by R were studied in 10 dogs. CO resulted in an abrupt fall in VFT from a control value of 63 ± 3 (S.E.) to 2 mA within 1.2 ± 0.1 min. Spontaneous recovery of VFT to control value occurred at 7.0 ± 0.1 min. Upon successive CO there was a progressive delay in the onset and decrease in duration of vulnerability. In comparison, R at 10 min resulted within 0.2 ± 0.1 min in a transient decrease of VFT to 2 mA. Repeated CO did not affect the time course of vulnerability changes during R. In 6 dogs the duration of CO was varied; 3 min of CO was the minimum time which resulted in reduction of VFT after R. In a series of 10 other dogs, propranolol (0.2 mg/kg) prevented decrease in VFT following 10 min CO but did not prevent change in VFT after R. The present findings support the view that the predisposition to VF produced by CO and R are mediated by different mechanisms; CO producing its effect through adrenergic factors; the basis for VF during R needs further definition, but may be due to washout products of cellular ischemia.

AUTONOMIC MANIPULATION IN THE INHERITED LONG QT-RECURRENT SYNCOPE SYNDROMES
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Regional autonomic dysfunction in the inherited long QT syndromes is suggested by experimental animal data, and a report of successful treatment in one case by unilateral stellectomy. However, results of stellate block in several other cases have been variable. This paper describes the results of right (R) and left (L) stellate block (SB) and percutaneous stellate stimulation (SS) in two symptomatic patients.

SS was performed using stimuli at 12 Hz and up to 5 Volts. SB was produced by 1% Xylocaine. A Horner's syndrome was seen with each block.

The results of the interventions on the rate corrected QT interval (QTc) are shown in the following table.

	SS			SB		
	CONTROL	RSS	LSS	CONTROL	RSB	LSB
Pt 1	0.52	0.59	0.52	0.53	0.51	0.47
Pt 2	0.50	0.50	0.50	0.50	0.46	0.46

It is seen that RSS in Pt 1 prolonged the QT interval, and that block of both RS and LS shortened the QT interval in both patients, being greater with LB in Pt 1. In addition, RSB in Pt 2 increased the heart rate from 70 to 95 beats/min. These results are different than expected from previous animal experiments. In the animals, RS ganglionectomy and LSS, but not LS ganglionectomy or RSS, produced QT prolongation, and RSS produced sinus tachycardia.

The results confirm that regional sympathetic dysfunction plays a role in these syndromes and suggests that the cardiac location of this dysfunction may differ in individual cases. In addition, the effects of SS in these pts are described, and the usefulness of this technic and SB in the evaluation of regional autonomic function is confirmed.

IMMEDIATE EFFECT OF CONTRAST INJECTION ON LEFT VENTRICULAR VOLUME. D.L.Vine, MD; H.T.Dodge, MD, FACC; D.K. Stewart, MD; J.A.Murray, MD, FACC. University of Washington, Seattle, WA

The immediate effect of injection of contrast medium on left ventricular (LV) volume and stroke volume (SV) was evaluated from the post-op LV biplane cineangiograms of 5 patients with 4-6 epicardial markers placed during coronary artery surgery. Spatial distances between markers were calculated for every cine frame of 7 consecutive beats beginning with the beat (0) preceeding injection of contrast. For each patient, the marker distances were related to angiographically determined volumes over one cycle (r=0.97-0.99). The regression equations determined from these relationships were used to compute LV volume from distances between the epicardial markers of beats prior to injection (0), during injection (1-4) and immediately after (5 & 6).

Control end-diastolic volume (EDV) (beat 0) ranged from 171-91 cc (mean=144cc). During injection (beats 1-4), maximum individual changes were small (+5, -10, -3, +8, & +2 cc) with mean changes (beats 1-6) of 0, +1, -2, -6, & -9 cc. The mean changes in end-systolic volume (ESV) (-1, -1, -3, -6, -7 & -9 cc), stroke volume (0, -1, +2, +4, +1 & 0 cc) and ejection fraction (EF) (0, 0, +1, +3, +3 & +4%) also show little change during injection. A relatively greater decline in EDV & ESV of beats 5 & 6 may be due to the valsalva effect seen in 3 patients but the injection, itself, produced no consistent change in LVEDV, ESV, SV or EF.

This is the first beat by beat analysis of the immediate effect on ventricular chamber volume of selective LV angiography and is an application of a new technique using epicardial metallic markers to quantitate LV volume changes.

IDENTIFICATION OF PREDISPOSING FACTORS TO VENTRICULAR ARRHYTHMIAS IN THE LATE HOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION. Louis A. Vismara, MD; James L. Hughes, MD; Dean T. Mason, MD, FACC; Robert Zelis, MD, FACC and Ezra A. Amsterdam, MD, FACC, Univ. of Calif., Davis

Since serious ventricular arrhythmias persisting late after acute myocardial infarction(AMI) may predispose to sudden death, factors associated with these arrhythmias were sought in this study. Holter(H) 8 hour monitoring was performed in 77 AMI patients(pts) during the ambulatory period of hospitalization(average 11 days post-CCU). H identified: group I(30 pts) with complicated ventricular(V) extrasystoles(PVC)(multifocal, paired, R on T, >5/min)in 26 of V tachycardia(VT) in 4; group II (25) with uncomplicated PCV; group III(22) without ventricular ectopy. The 3 groups were similar in age, sex, AMI location, coronary risk factors and CCU vital signs, X-ray cardiomegaly and extent of necrosis(Q waves and myocardial enzymes). Continuous CCU monitoring(3-5 days) in all groups revealed common prevalence of complicated PVC (14/30, 8/25, 8/22), and VT(5/30, 3/25, 3/22. Thus late hospital PVC are not related to CCU ectopy. CCU right heart catheterization showed no difference of the groups in cardiac index but I compared to III had higher pulmonary capillary wedge pressure(PCW)(14.3, 8.9 mmHg, $p<.05$) and lower systemic arterial pO_2(57, 70, $p<.05$). Post CCU (5-16 days) there were no group differences in Q and T waves, X-ray heart size, myocardial enzymes, serum cholesterol or medications. However hospital predischarge ST segment abnormalities occurred more frequently in group I than III(3.5, 1.3 leads/tracing, $p<.05$). Thus late hospital serious ventricular arrhythmias following AMI correlate with prior CCU arterial hypoxia and elevated PCW and with persistent ST segment abnormalities, suggesting that these rhythm disorders may be related to persistent myocardial ischemia and pump dysfunction.

RELATION OF VENTRICULAR ARRHYTHMIAS IN THE LATE HOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION TO POST-HOSPITAL SUDDEN DEATH. Louis A. Vismara, MD; James L. Hughes, MD; Jess Kraus, PhD; Nemat O. Borhani, MD; Robert Zelis, MD, FACC, Dean T. Mason, MD, FACC and Ezra A. Amsterdam, MD, FACC, Univ. of Calif., Davis, Calif.

To determine the prognostic significance of ventricular arrhythmias persisting during the hospital ambulatory phase of acute myocardial infarction(AMI), 64 AMI patients (pts) had continuous 8 hour Holter monitoring an average of 11 days after discharge from the coronary care unit (CCU). Pts were categorized according to ventricular ectopy: group I(27 pts) in whom extrasystoles(PVC) were complicated(multifocal, R on T, paired, $\geq$5/min) or had ventricular tachycardia(VT); II(22) had uncomplicated PVC; and III(15) had no ventricular arrhythmias. The 64 pts were followed an average of 25.8(13-38) months; there were 12 sudden deaths(SD), 8 deaths from other causes, and 44 survivors(S). All SD pts had ventricular ectopy recorded on hospital pre-discharge Holter(group I: 8 pts; II:4), while there were no SD in group III pts($p<.05$). SD and S pts were similar in age(60, 62 years), sex, location of infarction, coronary risk factors, severity of AMI(Q waves, cardiac enzymes), serum cholesterol, X-ray cardiomegaly, S_3 gallop and drug therapy. CCU arrhythmias did not separate SD from S pts: there were no differences in VT or ventricular fibrillation(3/12 pts, 6/44 pts) or complicated PVC(4/12, 12/44). Late hospital ECG revealed no differences in Q or ischemic T wave extent. However, SD pts had greater extent of ST segment abnormality than S pts(5.6, 1.8 leads/tracing, $p<.02$) suggesting their arrhythmias were related to persistent ischemia or segmental fibrosis. Thus ventricular arrhythmias persisting during late hospitalization for AMI are associated with subsequent sudden death.

MITRAL REGURGITATION IN PATIENTS WITH CORONARY ARTERY DISEASE: RELATION TO EXTENT OF MYOCARDIAL DYSFUNCTION. Louis A. Vismara, MD, Richard R. Miller, MD, Anthony DeMaria, MD, Dean T. Mason, MD, FACC, and Ezra A. Amsterdam, MD, FACC., Univ. of Calif., Davis, Calif.

To further investigate the mechanism and significance of mitral regurgitation(MR) caused by coronary artery disease(CAD), a group of 15 patients(pts) with major CAD-MR were compared to 15 controls(C) at coronary and left ventricular(LV) angiography. Pts were matched for age, sex, extent of CAD and all had markedly abnormal segmental contraction(ASC) of LV. LV diastolic volumes were comparably increased(MR 313, C 270 ml); however MR pts had a lower cardiac index(MR 2.3 $\pm$ .2, C 2.9 $\pm$ .3 L/min/M^2, $p<.05$); higher LV end diastolic pressure (mmHg) (MR 22.9, C 12 mmHg, $p<.01$). These hemodynamic differences did not result from MR alone since the LV ejection fraction was decreased (MR 25%, C 45%, $p<.05$). ASC, quantitated as percent of total LV perimeter (right anterior oblique), was greater in MR pts(MR 78%, C 53% $p<.05$). Since the extent of systolic akinesis and paradox in the two groups was similar it is uncertain if the greater hypokinesis (diminished systolic shortening) in MR pts was a manifestation of greater ischemia, and/or fibrosis. There was no difference in location of CAD, coronary collaterals, LV septal or lateral wall motion to explain the occurrence of mitral regurgitation. However, combined inferior and anterior wall ASC occurred in 13/15 MR but only 2/13 of C($p<.05$). Thus it is suggested that MR in stable CAD pts is directly related to the extent of LV with ASC and major MR occurs with combined posterior and lateral papillary muscle dysfunction. Furthermore, since major MR is associated with marked impairment in LV pump function, its presence indicates a poor prognosis.

THE EFFECTS OF METHYLPREDNISOLONE ADMINISTRATION ON CARDIAC PERFORMANCE AND ENERGETICS IN ACUTE INFARCTION.

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As large dosage corticosteroids have been shown to reduce infarct size experimentally, a study of the hemodynamic effects of methylprednisolone (MP) appeared indicated. MP 50 mg/Kg IV was given to 15 dogs instrumented with flowmeters with LAD ligation induced infarction & the results contrasted with 11 untreated animals. Ninety minutes after administration MP increased cardiac index from 0.72 to 1.06 L/min/m^2, arterial blood pressure from 55 to 66 mmHg, stroke work index from 3.49 to 9.43 gm-m/beat/m^2, LV max dp/dt from 1159 to 1531 mmHg/sec, coronary arterial flow from 13.2 to 23.5 ml/min, while coronary arterial-sinus O_2 difference narrowed from 11.7 to 9.1 vol%. Cardiac efficiency (SWI/MVO_2) doubled from 1.98 to 3.92 units Mean heart rate fell from 123 to 103 beats/min & coronary vascular resistance dropped from 4.14 to 2.10 10^5 dynes cm^{-5} sec. After 90 min, LVEDP, SVR & mesenteric, renal, femoral & carotid resistances were unchanged. In parallel cat papillary muscle experiments, MP had no effect on peak developed force, df/dt, time to peak force but reduced relaxation time. Following potentiation with paired stimulation, calcium & isoproternol, diminished force development & max df/dt were seen after MP. MP had no effect on adenyl cyclase activity. MP was thought to improve the critical oxygen balance by first dropping afterload & preload evanescently in the initial 15 min with heart rate & then increasing coronary arterial blood flow, with a resultant marked increase in cardiac efficiency & performance. The major dilatory effect of MP is thus in the coronary bed as other regional circulations remain uneffected.

ELECTROPHYSIOLOGICAL DELINEATION OF THE LEFT BUNDLE-BRANCH IN MAN

Albert L. Waldo, MD; Robert B. Karp, MD; Nicholas T. Kouchoukos, MD; William A. H. MacLean, MD; George K. Massing, MD; Thomas N. James, MD, FACC. University of Alabama, Birmingham, Alabama.

The concept that the left bundle-branch (LBB) divides into well defined anterior and posterior fascicles has gained wide-spread clinical acceptance despite lack of anatomical support. This concept was assessed in nine patients (pts) during open-heart surgery (aortic valve replacement) by electrographic delineation of the anatomical course and sequence of activation of the LBB. During normally conducted atrial rhythm, an electrode probe was used to record bipolar electrograms (EG) from selected sites on the left ventricular (LV) endocardium simultaneously with three ECG leads. The electrode probe was initially placed just below the junction of the noncoronary cusp of the aortic valve with the anterior leaflet of the mitral valve. The probe was then moved anteriorly along the LV septum by increments of 5 mm (the probe diameter) to a point just below the junction of the right and left coronary cusps of the aortic valve. Four such rows were mapped, each row one probe diameter below the other. Thus, EGs were recorded from LV endocardial sites up to 2 cm below the aortic valves. Specialized conduction system EGs were recorded in all four rows in all pts. The electrophysiologically delineated LBB cascaded as one broad undivided sheet down the LV from the membraneous septum. The anterior and posterior extent of the LBB varied from pt to pt. Discrete anterior and posterior fascicles could not be demonstrated from either the electrophysiological localization or sequence of activation of the LBB. Our electrophysiological data are consistent with the anatomy of the LBB as previously reported from this laboratory.

CURRENT INDICATIONS FOR MECHANICAL CARDIAC ASSISTANCE ON THE BASIS OF EXPERIENCE WITH 104 PATIENTS

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Clinical application of intraaortic balloon pumping (IABP) began in 1967 to evaluate its hemodynamic effectiveness and safety. Strict criteria were utilized to select 58 patients (pts) in medically intractable cardiogenic shock. Temporary shock reversal was observed in 84%; circulatory stabilization allowed cessation of pumping in 51%; 22% (12 pts) were discharged. Reevaluation over 6 years revealed: 7 pts well; 3 dead at 8-18 months from unrelated causes, 1 of acute myocardial infarction (AMI) at 2.5 years; condition of 1 is unknown.

With experience and understanding of physiology, indications for support were extended to: (1) Cardiac surgery - preoperative support in 10 "inoperable" pts with severe left ventricular failure (LVF) and mitral insufficiency; 6 pts for discontinuation of cardiopulmonary bypass (CPB), 2 assisted for late postoperative complications. Marked hemodynamic improvement was seen in the preoperative group (60% survival) and assistance in weaning from CPB was successful in 50%; (2) 13 pts with AMI, preshock, intractable pulmonary edema and terminal LVF were effectively supported for as long as 71 days (31% survival); (3) 5 pts with chronic LVF were evaluated for permanent mechanical assistance by diastolic augmentation; (4) 1 pt was successfully treated for intractable recurrent ventricular fibrillation (5) 4 pts with inoperable intractable angina pectoris were stabilized for 1-6 months; (6) 3 pts with gram-negative sepsis and shock showed no beneficial effect; (7) 2 pts were supported in attempt to reduce infarct size as measured by precordial mapping. IABP was found to be hemodynamically effective in all pts with LVF. Complications were rare (3%) and predominantly peripheral vascular.

PROPRANOLOL IN THE LONG-TERM TREATMENT OF ANGINA PECTORIS

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53 pts with stable, severe angina and CAD were studied prospectively with followup of 6-8yrs on propranolol hydrochloride (PH) to assess complication rate and long-term effectiveness after initial control period. Mean age was 56yrs; mean daily dose was 255 mg. Each pt had a dose threshold (between 160-480mg) at which maximum benefit was obtained. CHF had previously been documented in 21% and was compensated prior to PH therapy. 3 pts had a history of mild asthma. Average yearly mortality was 3.8% with a cumulative 5yr mortality of 18%. Pts with a $< 50\%$ reduction in pains on PH had almost a 4-fold greater mortality than those with $\geq 50\%$ decrease in pains ($p < .01$). 32% of pts/yr were angina-free on PH and 84%/yr had $\geq 50\%$ decrease in pains. There was no evidence for tachyphylaxis. CHF developed in 25% of pts, 68% of whom had either an acute MI(AMI) with CHF or previous CHF. All pts (4) with an initial C.T. ratio > 0.5 developed CHF during the first 3yrs of PH therapy. 12 pts on PH had an AMI during the study; 7 died, 6 with cardiogenic shock. Of 9 pts who developed CHF without AMI, 8 survived the initial episode. Significant side effects occurred in 19% and included CHF(6), GI symptoms(3), hallucinations (1), and postural hypotension(1). Some of the side effects not requiring drug discontinuation included transient eosinophilia(11),asthma(3),CHF(3)and 1st degree heart block(1).

PH is an effective form of long-term therapy for severe angina without tachyphylaxis and without increasing overall mortality, although it may increase the risk of cardiogenic shock in AMI. Previous CHF, a C.T. ratio > 0.5 without overt CHF, and mild asthma are relative contraindications. A $\geq 50\%$ reduction in pains on PH predicts a low mortality group.

MORTALITY FACTORS IN MYOCARDIAL INFARCTION - A FIVE YEAR STUDY

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Surgical alternatives in the management of coronary disease have made knowledge of natural history and prognosis vital in assessing risks and advantages of different forms of treatment. 212 patients with a confirmed diagnosis of acute myocardial infarction (MI) hospitalized 1967-68 were studied for 5 years. Factors associated with mortality were compared with those defined during the hospital phase. 46 (21%) of the original 212 patients died in the hospital. 10 were lost to followup. 43 (28%) of the remaining 156 patients died during the next 5 years. Acute phase mortality for anterior MI was 29% and for inferior MI 13%. 5 year mortality for anterior MI was 28% and for inferior MI 25%. Location affected acute but not long term prognosis. Patients with previous MI had a 36% acute mortality and 17% without prior MI. 5 year death rate for survivals of recurrent and first episode MI was 41 and 24% respectively. In-hospital mortality for intraventricular conduction defects (IVCD) was 47%, only 14% with normal IV conduction. Differential mortality was reduced for the next 5 years to 41% for IVCD, 25% without IVCD. Of 27 patients who left the hospital with IVCD, 12 had isolated left anterior hemiblock. 2 died. Of 15 with right bundle branch block, left bundle branch block or bifascicular block, 9 died. Among 11 patients with either LBBB or bifascicular block, 8 died. Attrition rate during the first posthospital year was very high accounting for 21 of the 43 deaths. The study identified mortality factors for a 5 year period after MI and showed that their prognostic significance differed materially from that during the acute hospital phase.

PERSISTENCE OF MYOCARDIAL INJURY FOLLOWING BRIEF PERIODS OF CORONARY OCCLUSION.

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Epicardial electrogram studies have suggested that ischemic injury caused by repeated 20 min coronary occlusions (occl) in dogs is completely reversible. To examine this in a mechanical analogue, regional function of the ischemic left ventricle (LV) was measured in 6 open-chest dogs using two mercury-in-Silastic segment length (SL) gauges sutured to the LV epicardium, one in an ischemic (I) area supplied by the transiently occluded left anterior descending coronary artery and another in a normal (N) area. Initial occl caused a systolic aneurysmal bulge and a loss of the systolic shortening phase (SSP). N-SL showed no change. Reflow for 45 min caused a gradual decrease in I-SL amplitude, but not to control levels, and the SSP abnormality persisted. Subsequent occl demonstrated a similar pattern in I-SL tracings. Measurements of I-SL amplitude gave the following results (Mean±SEM):

	Pre-occl	Occl (20 min)
1st occl	0.11±0.01	0.23±0.05*
2nd occl	0.19±0.04**	0.23±0.04*
3rd occl	0.18±0.02**	0.20±0.03*

($p<0.05$, *occl vs pre-occl; **2nd and 3rd vs 1st pre-occl; data expressed in muscle lengths (ML), where ML= peak SL/end-diastolic SL).

The results show that 1) persistent mechanical dysfunction is demonstrated after occl lasting 20 min, 2) prolonged injury results from periods of occl shorter than heretofore demonstrated, 3) regional mechanical changes are a very sensitive indicator of ischemic injury.

PLASTIC RECONSTRUCTION OF THE AORTIC ROOT FOR THE RELIEF OF CONGENITAL SUPRAVALVULAR AORTIC STENOSIS: POSTOPERATIVE EVALUATION

Daniel Weisz, MD; Alexis F. Hartmann, Jr., MD, FACC; Clarence S. Weldon, MD, FACC, Washington University, St. Louis, Missouri

Plastic reconstruction of the aortic root is accepted management for supravalvular aortic stenosis. An evaluation of this technique by postoperative left heart catheterization and aortography in a series of operated patients has not been previously available. Eight children (ages 3-15) have had a surgical correction of congenital supravalvular aortic stenosis. In 2 patients, an aortic valvotomy was also performed to relieve congenital valvular stenosis. Preoperative gradients in systole across the supravalvular lesion ranged between 40 and 90 mm.Hg. (average 70 mm.Hg.). In all patients, the aorta was incised longitudinally across the stenosis and down into the posterior sinus of valsalva to the aortic annulus. No tissue was excised. An ellipse of prosthetic cloth was inserted which purposefully separated the commissural attachments of the posterior aortic leaflet. Six of these patients have now been evaluated postoperatively. Postoperative gradients range between 0 mm.Hg. and 20 mm.Hg. (average 11 mm.Hg.). Angiographic appearance of the aortic root is near normal in all patients. Two patients have declined restudy, but all patients are asymptomatic. Properly performed plastic reconstruction of the aortic root provides an excellent correction of supravalvular aortic stenosis.

SURGICAL CORRECTION OF COARCTATION OF THE AORTA IN INFANCY: SPECIAL CONSIDERATIONS FOR INTRAOPERATIVE AND POSTOPERATIVE MANAGEMENT

Clarence S. Weldon, MD, FACC; Alexis F. Hartmann, Jr., MD, FACC, Washington University, St. Louis, Missouri.

Over a 4 year period, 15 infants under 1 year of age and with intractable congestive heart failure were operated upon for repair of coarctation of the aorta. Nine infants were under 2 weeks of age. The smallest infant weighed 1100 gms. There were 2 early postoperative deaths and one late death (1 mo. post hospital discharge) (Total survivals 80%). Six infants with associated intracardiac shunts had pulmonary artery bandings to control pulmonary blood flow. Improving results are attributed to (1) methods of postoperative management, (2) the adaptation of microsurgical technique to coarctation repair in infancy, and (3) the use of pulmonary artery banding performed immediately prior to coarctation resection whenever there is a large intracardiac shunt. This procedure controls pulmonary blood flow and prevents acute left ventricular volume overload during the time of aortic resection. Twenty patients from an earlier era who survived coarctation resection in infancy were studied in childhood. Six patients (30%) had severe anastomotic stenosis recreating the pathophysiology of coarctation. Second operations were performed in all 6 children. Resection of the anastomosis was done in 2 children and prosthetic grafting was performed in 4 children. Gradients were relieved in all cases and upper extremity hypertension has disappeared in all cases. With appropriate technique, surgical management of coarctation of the aorta in infancy provides excellent results. With growth of the child, anastomotic stenosis is a frequent complication. Second operations to relieve this stenosis by resection or bypass grafting can be performed with ease and provide excellent results.

RELATION BETWEEN REFRACTORY PERIOD OF THE ACCESSORY PATHWAY AND VENTRICULAR FREQUENCY DURING ATRIAL FIBRILLATION IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME.

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To assess the relation between the length of the refractory period (RP) of the accessory pathway (AP) and ventricular rate (VR) during atrial fibrillation (AF), two groups of patients (pts) with Wolff-Parkinson-White (WPW) syndrome, were studied. Group I consisted of 17 pts with documented episodes of AF. Group II was composed of 9 pts without a history of AF. In the latter group, following measurements of the RP of the AP, AF was induced by rapid atrial pacing (400 - 500/min). By way of the single test stimulus method (STSM) during atrial pacing the RP of the AP could be determined in 17 of the 26 pts. In 3 pts the RP of the AP was longer than 300 msec, in 8 pts in between 300 and 250 msec, and in 6 pts shorter than 250 msec. In 9 pts the RP of the AP could not be measured by the STSM, because the atrium became refractory at a time when AV conduction (AVC) was still occurring over the AP. In these pts regular atrial driving (AD) at increasing rates (up to 280/min) showed 1 to 1 AVC over the AP to AD rates of 240/min. in 2 pts and to 260/min in another 2 pts. In 5 pts 1 to 1 AVC over the AP was still present at AD rates of 280/min. A good correlation was found between the length of the RP of the AP and the shortest RR intervals during documented and induced episodes of AF. This indicates that measuring the RP of the AP is of value in identifying those pts with WPW who are at risk of developing life threatening high VR when AF supervenes.

REVERSAL OF ACUTE MYOCARDIAL ISCHEMIA BY RETROGRADE INTERCORONARY VENO-ARTERIAL PERFUSION

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In 15 dogs with hearts in situ, selective retrograde intercoronary veno-arterial perfusion (RIVAP) was established by anastomosis of a carotid artery to the cardiac vein draining myocardium supplied by the left anterior descending coronary artery (LAD). Pulsatile flow through this channel averaged 23.1 cc/min ±6.1 and was similar in wave form and quantity to that previously measured from the LAD (21.9 ±2.1).

Control measurements of the effects of ligation of the LAD prior to RIVAP were made. Circumflex artery blood flow did not change (ave. 31.0 cc/min ±7.3). Myocardial tissue pO_2 decreased -48.4% ±10.4 $p < 0.01$. Epicardial ECG ST segments increased +99.3% ±13.7 $p < 0.01$. Ventricular arrhythmia was invariable and required lidocaine for control. The region of myocardial ischemia became dyskinetic, manifesting paradoxical systolic expansion.

On the other hand, despite continued LAD ligation RIVAP significantly ($p < 0.01$) reversed myocardial hypoxia and the ischemic ECG effects. Myocardial tissue pO_2 returned to normal (-1.3% ±2.3). ST segment elevation decreased from +99.3% above baseline levels to +23.8% ±7.6. The myocardium supplied by RIVAP developed a normal contraction pattern and lidocaine was no longer required to control arrhythmia.

These experiments indicate that acute myocardial ischemia is reversed by RIVAP and suggest an alternative to aorto coronary bypass surgery.

ECHOCARDIOGRAPHIC PATTERNS OF PULMONIC VALVE MOTION IN PULMONIC STENOSIS

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Echocardiograms of pulmonic valves were obtained on 14 patients with catheterization proven isolated pulmonic stenosis (PS), 18 normal subjects and 65 patients with various forms of heart disease but no PS. Because of the plane of pulmonic valve motion and the angle of the ultrasonic beam, usually only one posterior pulmonic leaflet was recorded. In normal subjects atrial systole imparted a slight degree of posterior motion to this leaflet in late diastole (average 3 mm, range 0 to 7 mm). This atrial posterior motion varied with respiration and was not present with pulmonary hypertension. Without PS the leaflet always returned to a "closed position" prior to ventricular systole at sometime during the respiratory cycle. In patients with moderate or severe PS (gradient 50 to 142 mm Hg) the posterior atrial motion increased (average 10 mm, range 8 to 13 mm) and in patients whose gradient was greater than 65 mm Hg the pulmonic leaflet never returned to the "closed position" prior to ventricular systole. In mild PS (gradient less than 50 mm Hg) the degree of atrial opening of the leaflet fell within the normal range. The exaggerated posterior pulmonic leaflet motion following atrial systole is probably due to the increased right ventricular end-diastolic pressure together with a normal or decreased pulmonary artery pressure, producing a positive gradient across the valve following atrial systole. Although the pulmonic valves can be difficult to record echocardiographically, during this study there were only two patients with PS in whom satisfactory echoes were not recorded. These findings suggest that echocardiography may be helpful in the clinical evaluation of PS.

HEMODYNAMIC EFFECTS OF NITROGLYCERIN IN ACUTE MYOCARDIAL INFARCTION: DECREASE IN PRELOAD AT THE EXPENSE OF CARDIAC OUTPUT.

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Nitroglycerin (NTG) has recently been proposed to decrease myocardial ischemia and enhance cardiac pump function during acute myocardial infarction (AMI). Thus, the hemodynamic effects of sublingual NTG (0.4 mg) administered to 16 supine patients (pts) during the first 72 hrs of AMI were determined serially (5-10, 10-15, 20-30 min) over 30 min. Data were evaluated for the entire group (n=16) as well as for pts with normal pulmonary artery wedge (PAW) pressure (n=6)($\leq$12 mm Hg, mean 7) and pts with elevated PAW (n=10)($\geq$13 mm Hg, mean 19). Heart rate (HR) increased significantly in the normal PAW group (71→80, $p < .05$) but there was no change in the group with elevated PAW. In the entire group of pts, regardless of initial PAW, significant decreases ($p < .05$) occurred in: mean arterial pressure (MAP)(95→82 mm Hg), PAW (14→7 mm Hg), cardiac index (CI)(1.79→1.46 L/min/M^2), stroke index (SI) (24→18 cc/M^2) and stroke work index (SWI)(24→18 gm-M/M^2). There was no significant change in peripheral vascular resistance. Thus, in pts with AMI the major effect of NTG was to reduce preload with subsequent decrease in SI, CI and MAP. Pts with normal PAW responded with an increase in HR. The lack of increase in HR in pts with elevated PAW may be due to attenuated sympathetic reflex function which we have documented in AMI. NTG is effective in decreasing hemodynamic determinants of myocardial oxygen demand, especially in those pts with pulmonary congestion, but this occurs at the expense of cardiac output. Its use in AMI, therefore, requires careful pt selection.

THE HEMODYNAMIC RESPONSE TO SUBLINGUAL ISOSORBIDE DINITRATE IN UNSTABLE ANGINA PECTORIS

William H. Willis, MD; Richard O. Russell, Jr., MD, FACC; John A. Mantle, MD; Robert A. Ratshin, MD; Charles E. Rackley, MD, FACC; University of Alabama, Birmingham, Alabama.

The sustained supine hemodynamic response to 10 mg sublinqual isosorbide dinitrate (IS) in comparison to that of a sublingual placebo (plbo) was measured in 15 patients with unstable angina. Alternately eight patients received IS and seven plbo. A Swan-Ganz thermodilution catheter was positioned in the pulmonary artery (PA). PA systolic (PASP) and end-diastolic pressures (EDP), heart rate, thermodilution cardiac output, echo end-diastolic volumes (EEDV), and cuff arterial blood pressures were measured at five min intervals for the first 30 min then every 30 min for a total of four hrs. Cardiac index (CI), stroke index (SI), stroke work index (SWI), mean arterial blood pressure (MAP), and total systemic resistance (TSR) were calculated. The mean change in these hemodynamic parameters was compared at each time period between the IS and plbo groups. The mean significant ($p<0.05$) difference in systolic arterial pressure (SAP) was -16 to -18 mmHg from 30 min to two hrs. The MAP mean significant ($p< 0.05$) difference was -9 to -15 mmHg from 30 min to four hrs. The PASP mean significant difference ($p<0.05$) was -6 to -8 mmHg from 10 min to 90 min. The significant ($p < 0.05$) mean PAEDP difference was -4 mmHg at 60 min. CI, SI, SWI, EEDV, and TSR demonstrated a similar reduction after IS; however, because of a large patient to patient variation, these values did not reach significance. The duration of IS reduction in SAP and PAEDP was six times longer than that after sublingual nitroglycerin in a reported study from this laboratory. Sublinqual IS causes a prolonged decrease in both left ventricular preload and afterload in patients with unstable angina.

LONG TERM PERVENOUS CORONARY SINUS PACING

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Permanent transvenous coronary sinus pacing was found to be effective, relatively stable and surprisingly free of complications in 21 of 23 patients with sick sinus syndrome, bradycardia-tachycardia syndrome and carotid sinus syncope. In two cases, it was not possible to position the catheter in the coronary sinus. Partial or complete relief of symptoms was achieved in 90 percent of patients and all but 1 became free of syncope, dizziness and weakness. Complicating ectopic arrhythmias were controlled in all but one patient. An unexpectedly high incidence of angina was encountered (63%) which responded to pacing alone in 6 of the patients. No evidence of atrioventricular (A-V) block or intraventricular conduction defect was observed during the follow-up period. No major complications of rupture, thrombosis, embolism, myocardial injury, new arrhythmias or ischemia were identified after 243 patient months of follow-up. Although thresholds were initially high ($\pm$ 3.0 mA), exit block problems did not develop with time, and 6 of 7 patients who had pacemaker replacements showed no significant threshold change.

Satisfactory atrial capture was ultimately attained in all but 1 patient (who developed chronic atrial fibrillation.) Sensing problems were common but relatively innocuous and they have not produced clinical symptoms nor have they interfered with long term benefit to the patient. Most sensing problems could be eliminated by a pacemaker with a refractory period of more than 300 msec; this would eliminate inconsistent sensing of QRS of paced beats.

COMPLICATIONS OF CLOTH-COVERED PROSTHETIC VALVES

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Following experiments in 1967 with cloth-covered prosthetic valves, a number of investigators including Braunwald, Starr, Spencer and others have advocated their use. The principal advantage offered by such valves is a decreased incidence of thromboembolism.

Complications, however, have included cloth wear, hemolysis, increased pressure gradients compared to other prostheses, "stuck ball syndrome" and a rare intractable infection. Stenosis at the prosthesis is related to the added bulk compared to noncloth-covered valves.

In our experience with 4,235 valve replacements, the completely cloth-covered prostheses have proved unsatisfactory. Hemolysis was higher as demonstrated by lower mean hematocrit levels and higher mean reticulocyte and LDH values. Cloth wear over the struts, in particular, has occurred with unacceptable frequency. Hemolysis usually results from a jet of blood striking an unendothelialized fabric surface, and cloth-covered prostheses subject the blood to this undesirable condition.

A new mitral prosthesis has been designed which eliminates this undesirable characteristic and incorporates certain favorable features. The surfaces exposed to the jet stream are highly polished titanium and pyrolitic carbon. Other desirable features include a low profile, low gradient, full-orifice opening and a "self-washing" principle due to the controlled leakage around the periphery of the poppet. Experience with more than 300 valve replacements with this prosthesis will be reported.

A LARGE KINDRED WITH FAMILIAL TYPE II HYPERLIPIDEMIA WITH MINIMAL CLINICAL CARDIOVASCULAR DISEASE

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The kindred under investigation to our knowledge is the largest to be reported with familial type II hyperlipidemia. The large midwest kindred has fifteen siblings, 279 individuals and 222 direct line relatives which were evaluated for familial hyperlipidemia.

Tendinous xanthomas were present in 4 members, xanthelasma in 2, one a 10 month boy. There has been one death following coronary artery bypass surgery and an additional member of the family had a myocardial infarction at age 58.

When the serum cholesterol values were age adjusted 32 had abnormal lipid values, 24 with Fredricksons type II_A and 8 with Fredricksons type II_B.

Genetic analysis of this pedigree reveals evidence for a single autosomal dominant gene producing hyperlipidemia characterized by elevated levels of cholesterol and triglycerides, xanthomas and a reduced degree of severe clinical cardiovascular disease. A bimodal distribution of cholesterol level was found in direct-line relatives of first generation affected but not in the direct-line relatives of first generation normals.

In this large kindred with familial type II hypercholesterolemia, out of 32 individuals with hyperlipidemia only 2 have had evidence of clinical cardiovascular disease.

RESULTS OF CORONARY BYPASS SURGERY FOR THE TREATMENT OF CORONARY INSUFFICIENCY.

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Aorto-coronary anastomosis was performed in 851 patients, with a total of 1496 anastomoses. Saphenous vein bypass was used in 831; of these, 41.5% received one bypass, 40.5% two, 17.4% three, and 0.6% four bypasses. Fifteen patients were treated with mammary artery-coronary anastomosis, and five had combined procedures.

Chronic coronary insufficiency was present in 85.6% of the patients, 10.6% of the patients were considered to have impending infarction, and 3.8% had acute myocardial infarction. Immediate and late mortality had no relation with the number of bypasses performed. Late post-operative results were influenced by the number of diseased arteries and by the pre-operative ventriculogram. Post-operative cine coronary angiography, performed in 273 patients with a total of 331 bypasses, demonstrated 90.3% patency. Of these, 201 patients operated on in the last two years had 93% patency. Post-operative myocardial infarction was observed in 6.4% of the patients, observed up to 45 months. Of these, 44.7% became asymptomatic after the infarction and 42.1% failed to survive.

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Women with chest pain and normal coronary arteries, 168

Keeps you right on the button.

The freeze and record buttons on our four-patient monitoring station are where they can be pushed most quickly and most accurately:

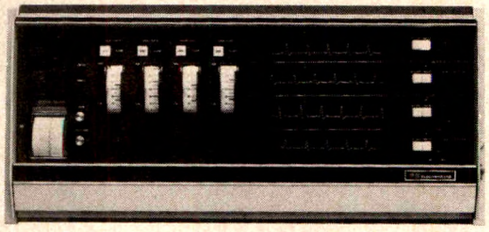
Right alongside of each patient's trace. Not the traditional distance away, with the traditional potential for error.

Unusual design thinking? Not at B-D—Becton, Dickinson and Company. We try to make all our equipment safe, efficacious, reliable and easy for the operator to use properly and promptly. We call that Operator/Machine Interface. The buttons are just one example. There are dozens of others.

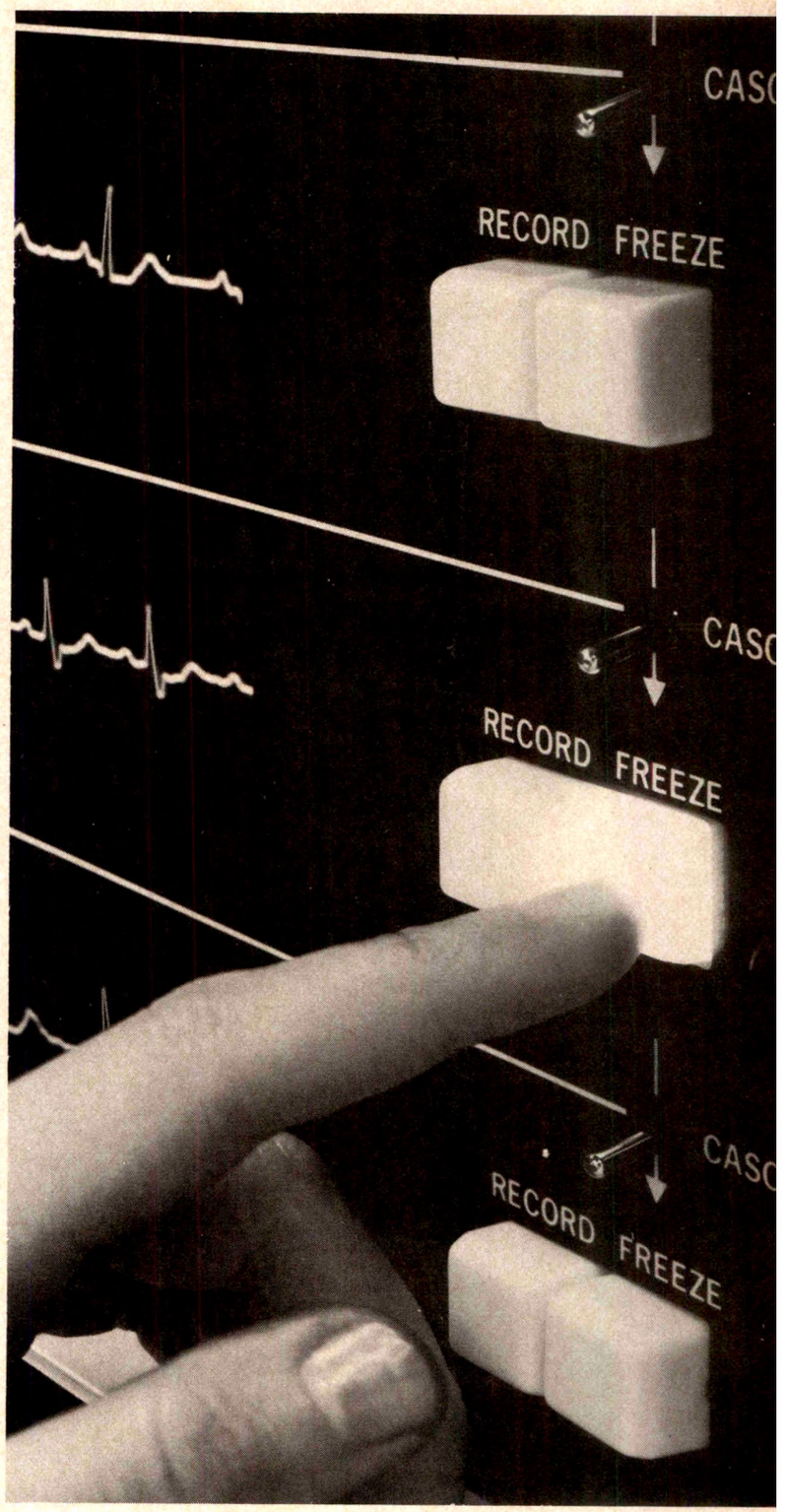
You see, we know your problems firsthand. We have a large, full-time staff of MD's. And no new product leaves our place unless the MD's have approved it.

Maybe that's how B-D Electrodyne got to be the foremost supplier of ICU/CCU monitoring systems in the country. Why not let us send you our catalog?

B-D ELECTRODYNE, Division of Becton, Dickinson and Company, Sharon, Mass. 02067. (617) 828-9080.



B-D **ELECTRODYNE**
Division of Becton, Dickinson and Company



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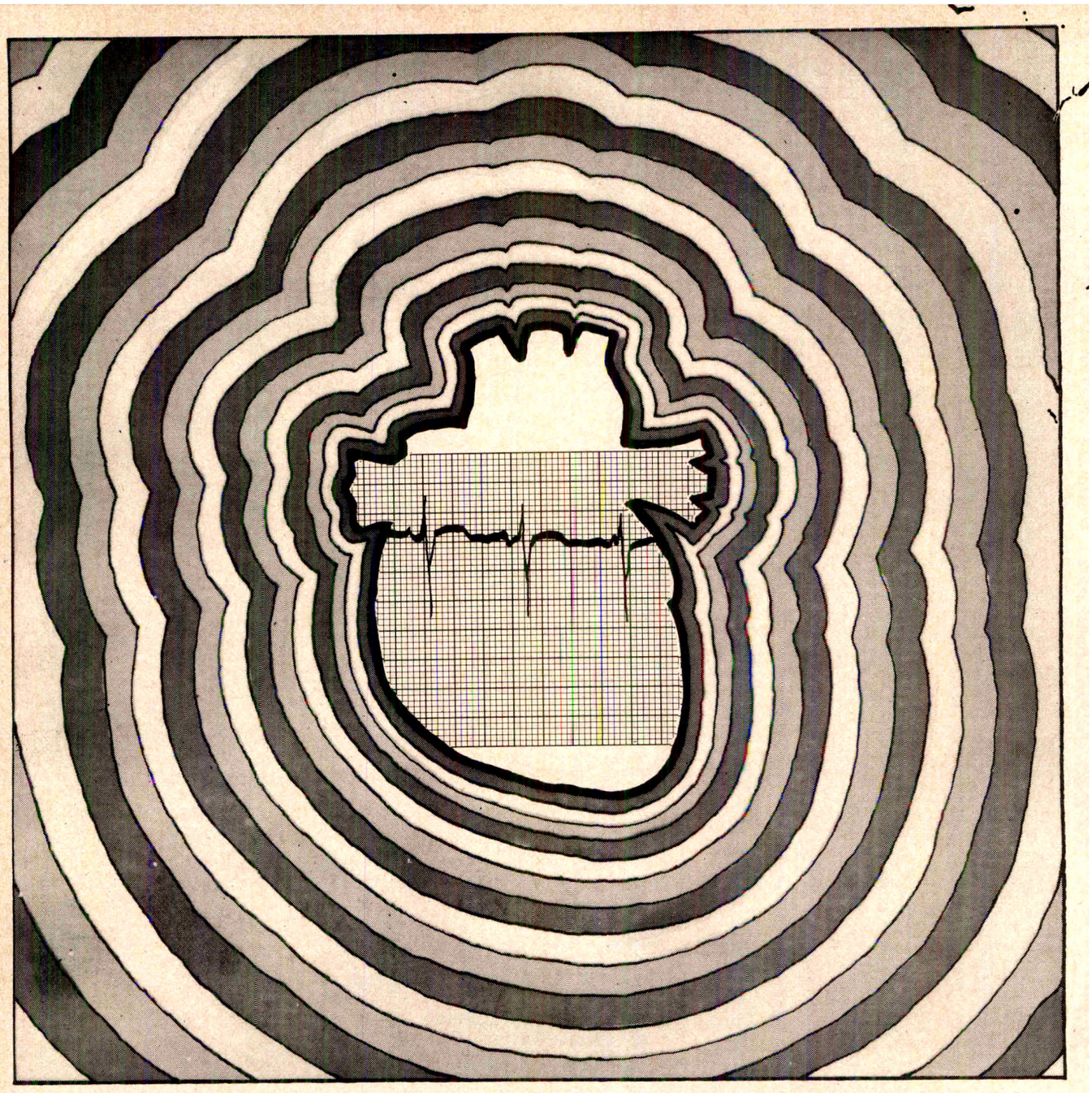

the heart of your electrocardiograph diagnosis is made of paper

Accurate interpretation of analytical data presented by your electrocardiograph and subsequent proper diagnosis is manifested by the chart paper.

If there's a chance the chart paper is lacking in quality or accuracy, an inaccurate recording may well be the result.

Why take the chance. Specify the paper designed and produced expressly for the manufacturer of your instrument. The cost of total assurance simply isn't worth the few pennies substitutes may save.

This message was prepared in the interest of better recording instrument performance by . . .

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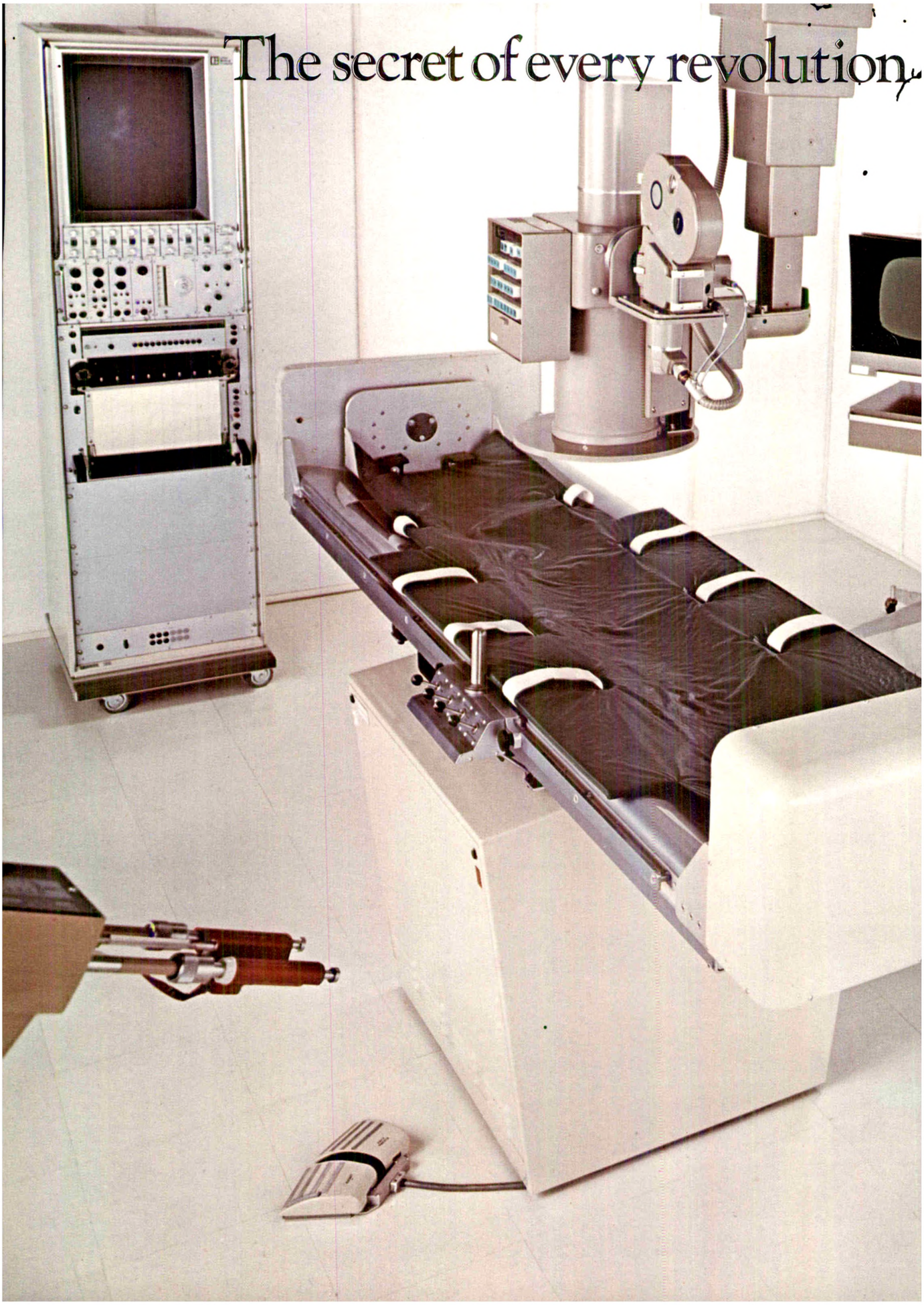
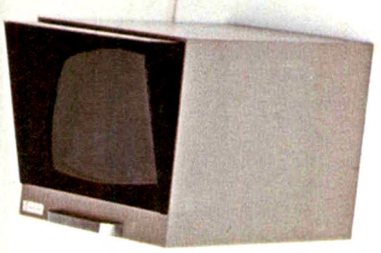

The secret of every revolution.

is effective use of power.



The revolutionary Profexray Lab-2 Ciné System is an integrated cath lab that doesn't require a separate control.

Every institution with a heavy patient load for heart-cath work could use a back-up lab. And a lot of smaller institutions would like to add ciné-angiography to their capabilities for a realistic investment. We've just answered these two needs.

Introducing the Lab-2 Ciné room.

A complete, self-contained system that doesn't need a complex, high-powered generator. Everything you *do* need—in controls, instrumentation and power—is right there in the Lab-2—built around the finest ciné system in the world. It's streamlined for maintenance and service. It's systems-engineered and pre-tested *before* installation. We're so certain of its unmatched reliability that Lab-2 is backed by a full two-year warranty.*

It's another part of the Profexray radiology revolution: equipment and concepts to completely overthrow an old order of doing things, and give you new standards of efficiency.

Get in touch with your Profexray representative for the details on the Lab-2 Ciné System. You'll find him a powerful ally.

Litton **PROFEXRAY**
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Litton technology: The 2nd American Revolution.

*The two-year warranty applies to all Profexray-manufactured equipment. X-ray tubes and image intensifiers are subject to manufacturers' warranties.

Processall gives you two keys to accurate diagnosis in Cine Fluorography.

High quality results. Fast processing.

In cine fluorography, you want fast results – but not at the price of fuzzy film detail. The Processall gives you fine grain yield, superior resolution for a sharp image and all the detail you need for an accurate diagnosis. With automatic processing and speeds up to 8 feet per minute, you get results fast.

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A simple drive system and 316L stainless steel construction ensure complete reliability, long life, and minimum maintenance. Processall is designed for flawless high quality results. It includes a turbulent agitation processing technique, thermostatic control of solution temperature and an air impingement squeegee that removes moisture before the film or paper enters the turbulent heated air drying chamber. A positive drive, with a demand drive guarantees positive tracking. Electrocardiograph paper may also be processed.

No wonder major medical centers and hospitals are now using Processall. For more information contact us, or your nearest Oscar Fisher dealer.

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a new face in the cath lab

SERIES **939**

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Mennen-Greatbatch now offers a wide variety of systems to meet modern trends in cardiovascular diagnostics. They include advanced instrumentation for invasive and non-invasive procedures such as heart sound studies, His bundle electrograms and pulse cardiogram studies. MG also offers complete computerized systems and computerization for existing equipment to speed calculations and supply instant display of data. For more information, contact your local MG representative or Mennen-Greatbatch Electronics, Inc., Clarence, N.Y. 14031 U.S.A.

Convenient mobile consoles have functional instrument arrangement and work surface.

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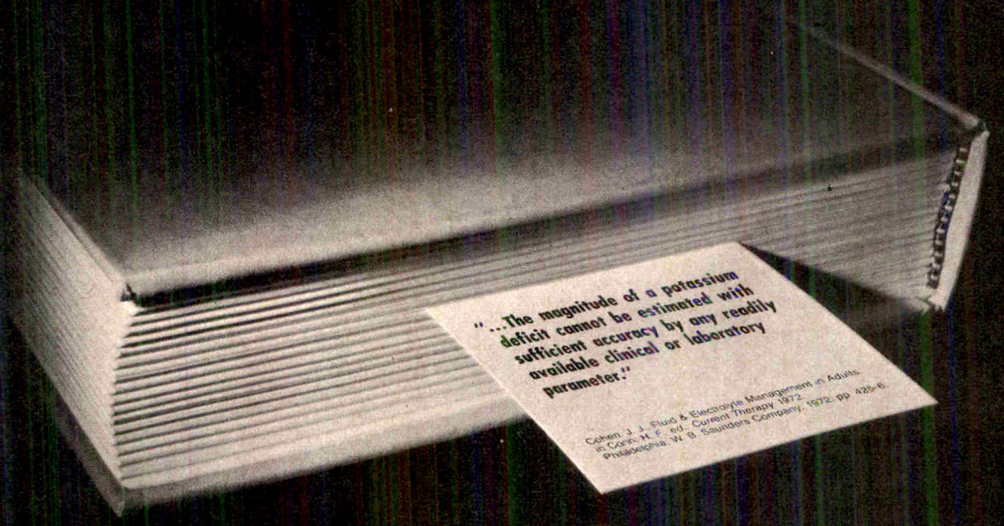
Help prevent this common thiazide and furosemide problem:

HIDDEN HYPOKALEMIA



Prescribe good-tasting

K^+LORVESS®

effervescent tablets

Each tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g.

1:1 ratio K^+ and Cl^- in solution

SIMPLE TO TAKE—Tablets dissolve in 3-4 oz. cold water
SPARKLING TASTE APPEAL—Fruitlike flavor
PATIENT ACCEPTANCE—Reduces chance of G.I. irritation. No added calories.
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KLORVESS offers what you and the patient like

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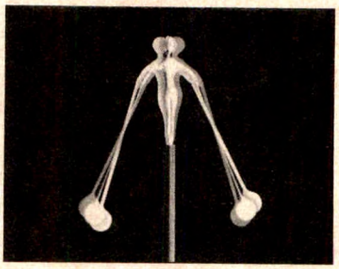


KLORVESS®
Effervescent Tablets

Description: Each dry effervescent tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g. Solution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate, and l-lysine hydrochloride.

Indications: For prevention or correction of potassium depletion and hypokalemic alkalosis. Especially useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each tablet completely in the stated amount of water.

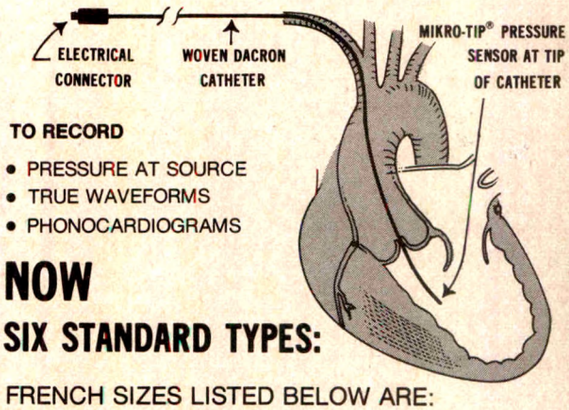
Adverse Reactions: Vomiting, diarrhea, nausea and abdominal discomfort may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, and tall, peaked T waves.

Dosage and Administration: Adults: 1 tablet (20 mEq. each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water 2 to 4 times daily depending upon the requirements of the patient. The approximate minimum adult daily requirement of potassium is 40 mEq. Deviations from this recommendation may be indicated, since no average total daily dose can be defined but must be governed by close observation for clinical effects.
NOTE: Klorvess should be taken with meals.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

How Supplied: Klorvess Tablets (white, round) in boxes of 60 (2 Rx units of 30, NDC 43-100-87). Each tablet is individually foil wrapped.

MILLAR MIKRO-TIP®
CATHETER PRESSURE TRANSDUCERS



TO RECORD

- PRESSURE AT SOURCE
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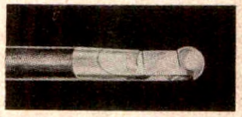
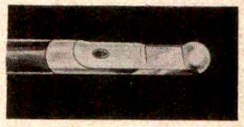
NOW
SIX STANDARD TYPES:

FRENCH SIZES LISTED BELOW ARE:
5F=1.67mm o.d., 7F=2.33 mm o.d., 8F=2.67 mm o.d.

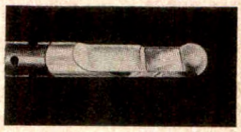
SINGLE PRESSURE SENSOR.
Available in 5F, 7F and 8F sizes



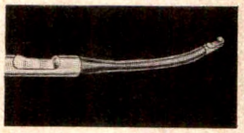
SINGLE PRESSURE SENSOR WITH LUMEN FOR BLOOD SAMPLING, EXTERNAL PRESSURE MONITORING OR SLOW DYE INJECTION.
Available in 7F and 8F sizes



SINGLE PRESSURE SENSOR WITH LUMEN FOR HIGH SPEED INJECTION OF RADIOPAQUE CONTRAST DYE.
Available in 7F and 8F sizes



DUAL PRESSURE SENSORS FOR SIMULTANEOUSLY RECORDING OF PRESSURE AT TWO LOCATIONS. Available in 7F and 8F sizes, 5F size between Distal and Proximal Sensors



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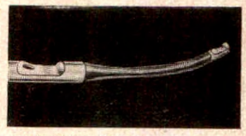
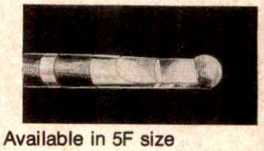
Available in 7F and 8F sizes, 5F size between Distal and Proximal Sensors



SINGLE PRESSURE SENSOR WITH DUAL ELECTRODES FOR RECORDING PRESSURE WHILE STIMULATING WITH OR RECORDING FROM THE ELECTRODES. Available in 5F size



Transducer Control Units are available for interfacing with most recorders or display systems.

MILLAR INSTRUMENTS, INC.

P.O. Box 18227 (6001 Gulf Freeway) Houston, Texas 77023 U.S.A. (713) 923-9171

[illegible] ium [illegible]ent from cheating themselves.

Most salt substitutes have an unpleasant metallic aftertaste. Not Adolph's. It really seasons like salt. It's granulated, too. Comes in a shaker bottle. So it looks and sprinkles like salt. The flavor won't fade in cooking, either. And it contains mono-potassium glutamate to enhance the natural flavor of food.

Adolph's Salt Substitute contains less than 1 mg. of sodium per teaspoon, and it's a valuable source of supplemental potassium.

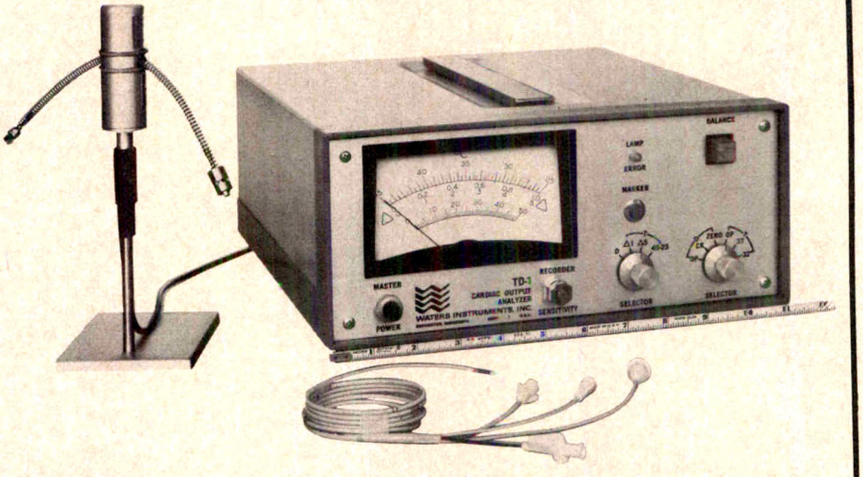
It's sold at food stores in two varieties—

Regular: Potassium chloride, glutamic acid, mono-potassium glutamate, silicon dioxide, tartaric acid, potassium iodide .01%.

Seasoned: Potassium chloride, sugar, spices, mono-potassium glutamate, glutamic acid, silicon dioxide, tartaric acid, vegetable oil.

For free physician's samples, write to Adolph's Ltd., P.O. Box 828, Dept. SM, Burbank, California, 91503.

Now... Thermal Dilution Capability with a Dichromatic Densitometer



The Waters TD-1 Cardiac Output Analyzer measures cardiac output via thermal dilution as well as dye dilution. This dual capability allows for the determination of cardiac output at frequent intervals over long periods and, in addition, provides accurate dye dilution measurements.

The Waters Dichromatic Densitometer has always been in a class by itself, because it not only reads the primary dye pattern but also considers artifacts and neutralizes their impact on measurement readings.

The addition of thermal dilution capability makes the Waters TD-1 the most accurate, versatile and advanced indicator dilution instrument available.

See the Waters TD-1 at the American College of Cardiology Convention in New York February 11-14 Booth 154

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(isosorbide dinitrate)

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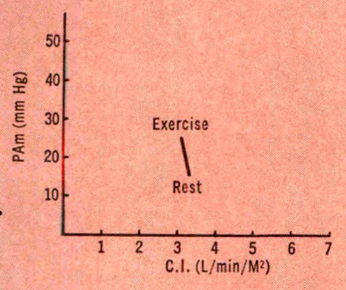
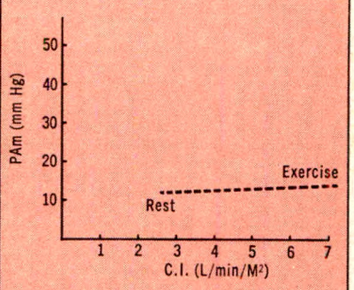
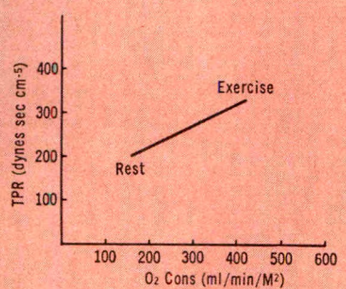
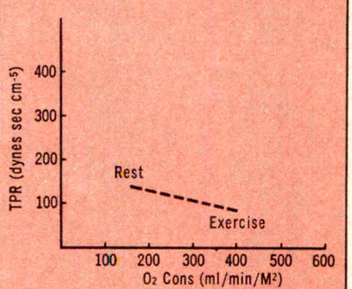
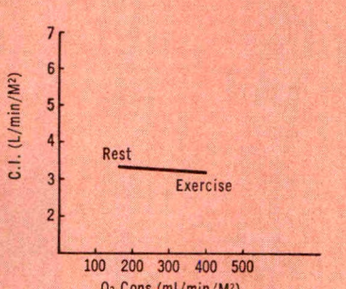
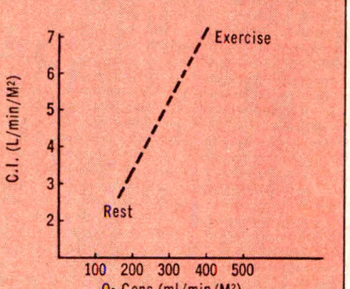
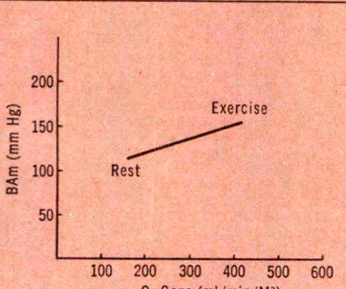
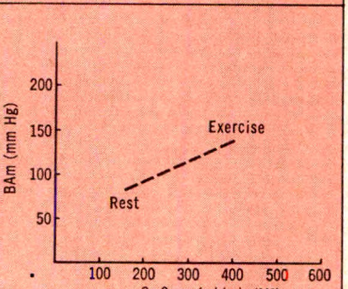
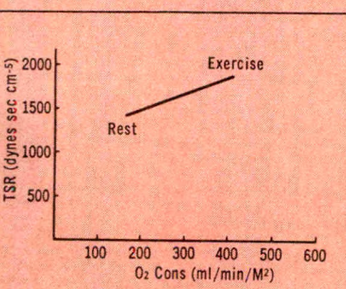
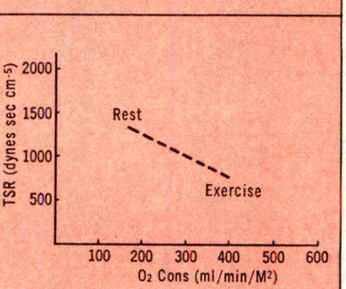
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

IN ANGINA PECTORIS*

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday stress

ISORDIL® SUBLINGUAL
(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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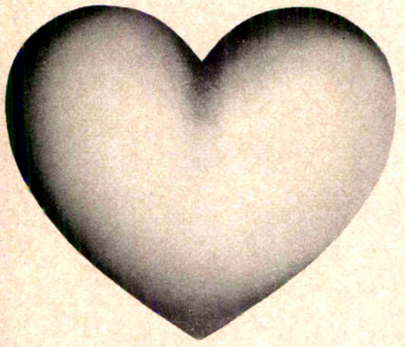
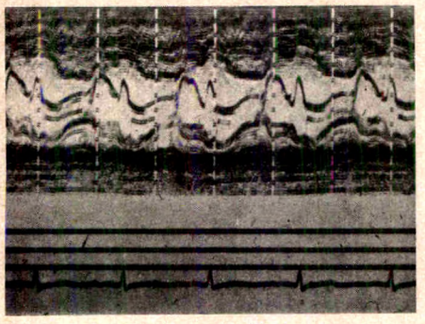
New York, N.Y. 10017
DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.

Ultrasound. Who needs it?





Heart scan on Echoview™ X showing prolapsing mitral valve. Photo courtesy Dr. Fred Winsberg, Montreal General Hospital, Montreal, Quebec.

You do. And your patients do. For ultrasound is opening new vistas in diagnostic visualization. In fact, it's the fastest-growing of the more important imaging technics. (We know because we also make the other major types—both radioisotope and x-ray imaging systems.)

But why Picker ultrasound? A fair question to which there are several good and valid answers.

1. Picker has been the pioneer and leader since we introduced ultrasound equipment in this country a decade ago.
2. Picker equipment has stood the test of time. Picker continues in its leadership role by innovative design and thorough field testing. In fact, more ultrasound scans are made with Picker equipment than with all other scanners combined.
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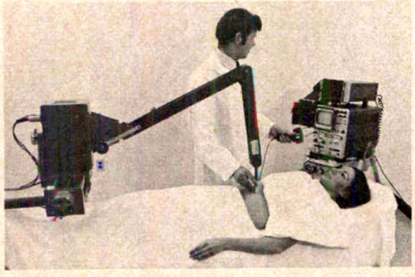

Longitudinal view of near-term anencephalic fetus. Photo courtesy Dr. George Leopold, University of California, San Diego, California.

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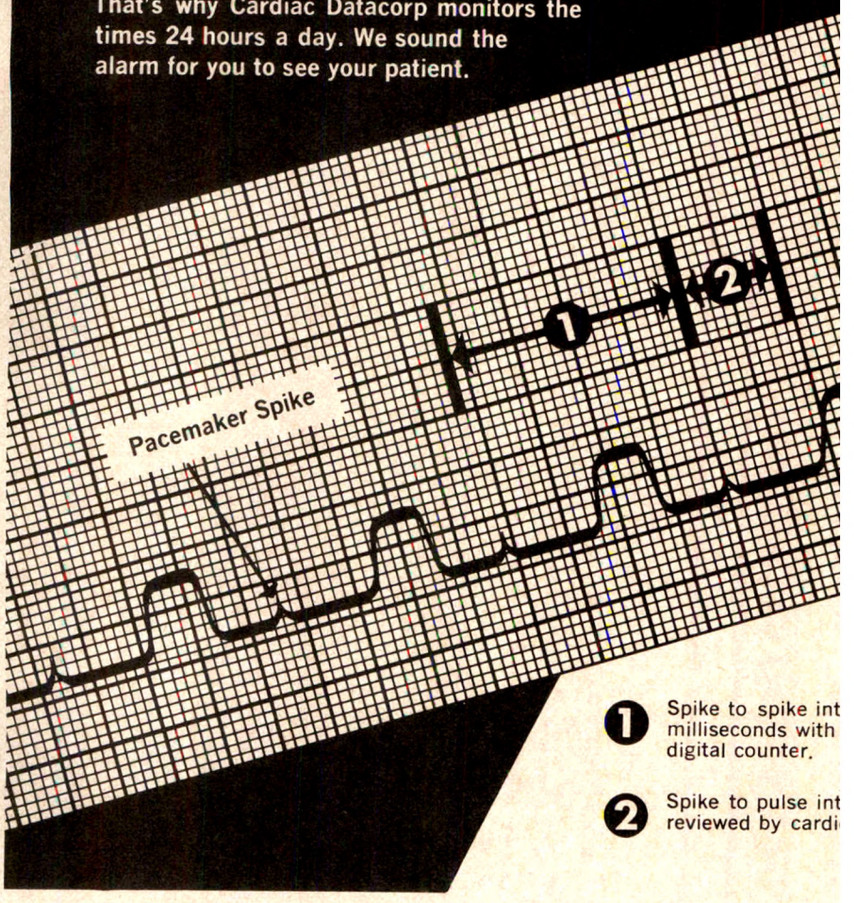

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Description: Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates, may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur. In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature: (a) Cutaneous vasodilatation with flushing. (b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. (c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later.

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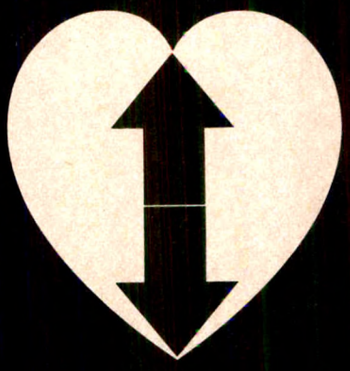
Concerned about over or under digitalization?



Then speak to your laboratory—they can now help you monitor digoxin and digitoxin blood levels.

Clearly the digitalis glycosides have been a mixed blessing. Their potential for good is inevitably coupled with the possibility of harmful effects due to inadequately low or toxically high blood levels. And then, as if the narrow margin of safety weren't enough, we also began to realize that there are variations in bioavailability of these glycosides. From glycoside to glycoside. From company to company. From one route of administration to another. From dosage form to dosage form. Sometimes even from lot to lot.

Yet, despite these multiple uncertainties, no really practical tool existed for monitoring digitalis glycoside blood levels. The result, according to some observers, can be serious. One worker stated that perhaps 20 to 25% of all digitalized patients are actually overdigitalized to the point of toxicity and that this situation had reached epidemic proportions.[1] Another reported that the mortality rate from overdigitalization ranges from 3% to 21%.[2]

And in the same study, 11% of the digitalized patients previously thought to be on adequate daily maintenance therapy were actually shown to be *underdigitalized.* One recent report indicated that while an oral digoxin solution was completely absorbed, a digoxin tablet was only 75% absorbed.[3]

Those are the problems. Now the news here is this: new radioimmunoassay techniques have been developed for monitoring digoxin and digitoxin blood levels. These are perfectly practical methods that offer exceptional sensitivity and specificity. So, if you're concerned about the problems of overdigitalization and underdigitalization, speak to your laboratory about the availability of these new radioimmunoassays. They can help minimize a serious problem. Perhaps you'll also be interested to know that we supply radioimmunoassay kits for renin activity and vitamin B_{12} determinations. These, too, are characterized by unusual sensitivity, specificity and precision. Once again, speak to your laboratory. For further information, write Schwarz/Mann, Mountain View Avenue, Orangeburg, New York 10962.

(1) J. F. Doherty, *Annals of Internal Medicine,* May 1971.
(2) G. A. Beller, et al., *New England Journal of Medicine,* May 6, 1971.
(3) D. H. Huffman, et al., *JAMA,* November 20, 1972.

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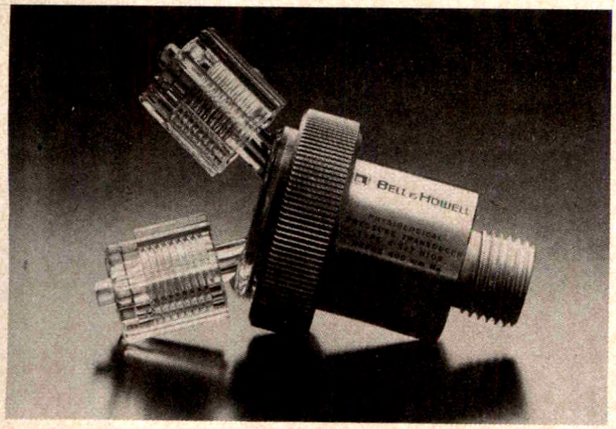

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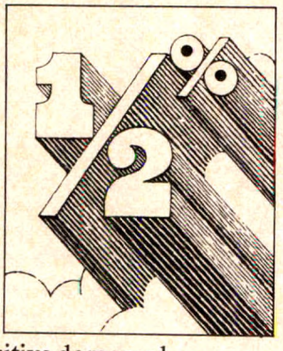

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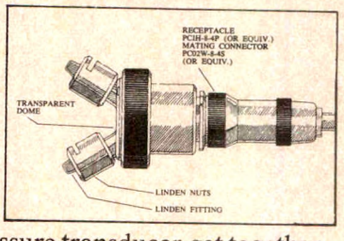

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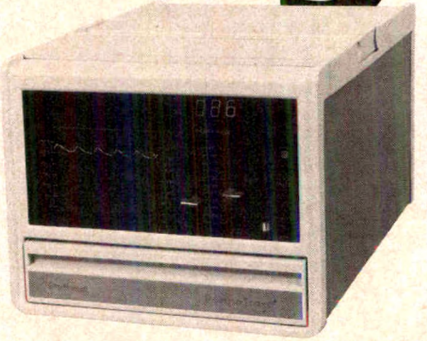

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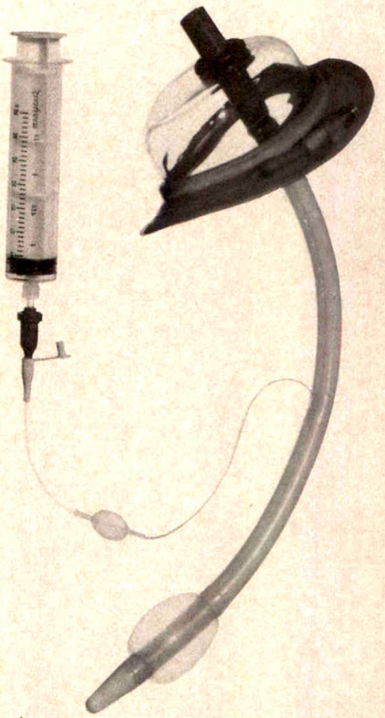
- Does not require visualization of the larynx or esophagus.
- Does not require any interruption of CPR.

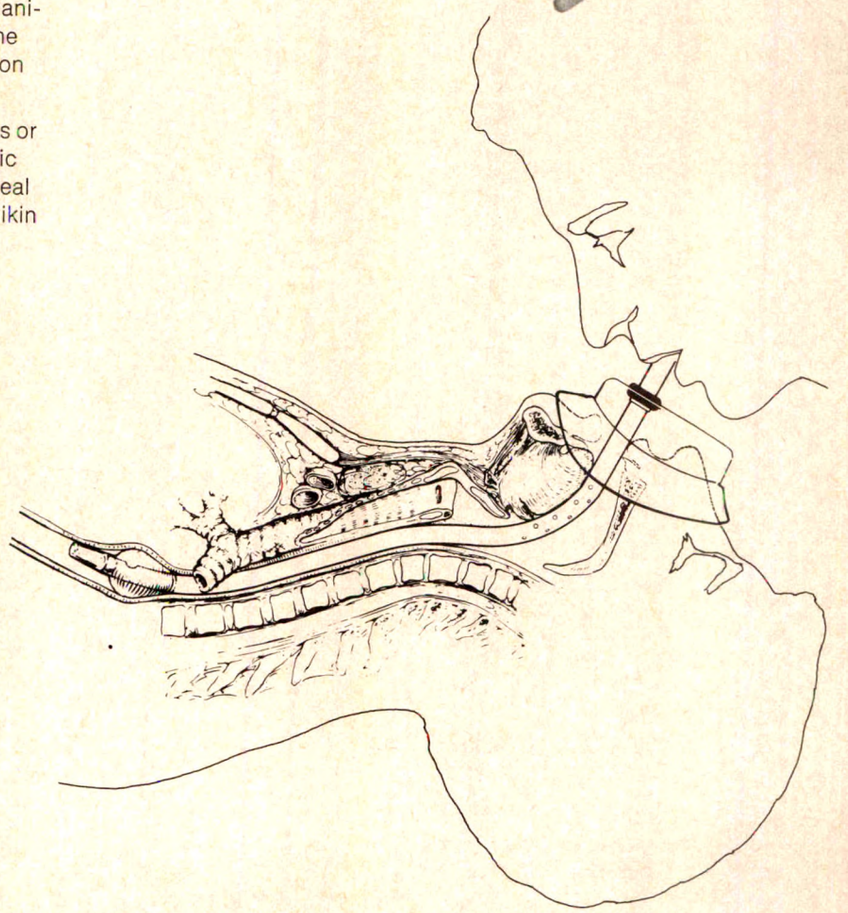
When the airway is inserted and the mask is seated on the face, the obturator tip and inflatable cuff lie in the esophagus below the bifurcation of the trachea. The tip and inflated cuff occlude the esophagus and:

- Prevent gastric distension during resuscitation.
- Prevent regurgitation which leads to aspiration of gastric contents.

Mouth-to-mask, bag-valve-mask, or mechanical ventilation at the mask orifice inflates the lungs via the multiple openings in the portion of the airway which lies in the pharynx.

Contraindications: 1. children; 2. conscious or semi-conscious patients; 3. cases of caustic poisoning; 4. patients with known esophageal disease; 5. rescuers without adequate manikin and/or clinical training and practice.





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1. Don Michael, T. A., Lambert, E. H. and Mehran, A.: Mouth to Lung Airway for Cardiac Resuscitation. *The Lancet*, 2:1329, December 21, 1968.
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5. Esophageal Obturator Airway, in *Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC), 1973*, American Heart Association/National Research Council, 1973, p. 25-27.
6. Farley, M.: The Esophageal Obturator Airway. *Respiratory Therapy*, Vol. 3, No. 6, November 1973, p. 95-99.

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Pronestyl® Capsules/Injection
(Procainamide Hydrochloride)

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 g. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

How Supplied: Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg. and 500 mg. are available in bottles of 100 and 1000 and Unimatic* Single Dose packaging in cartons of 100. Capsules providing 375 mg. are available in bottles of 100. Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) providing a 10% sterile aqueous solution (100 mg./cc.) with 0.9% (w/v) benzyl alcohol is available in 10 cc. vials.

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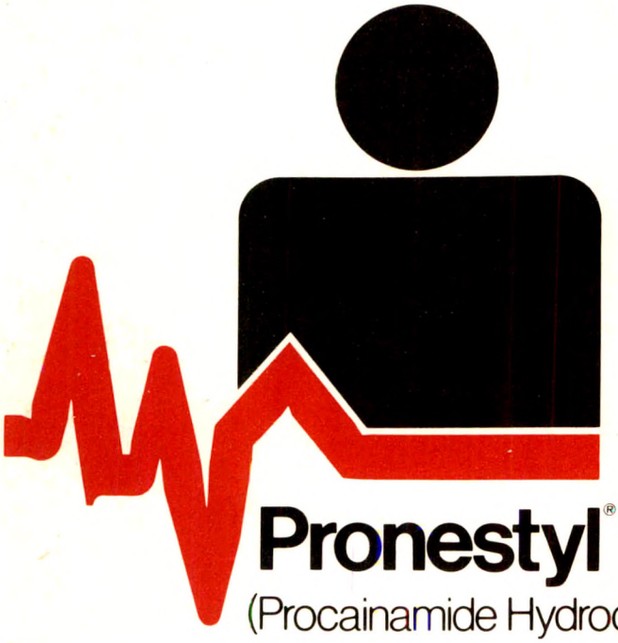
At the first sign of trouble



Pronestyl®

(Procainamide Hydrochloride)

for premature ventricular contractions

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'The Priceless Ingredient of every product is the honor and integrity of its maker.'™

See opposite page for brief summary.

"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

Kay Ciel® Elixir is potassium chloride... tastes good too!

COMPOSITION: Each 15 cc. (one tablespoonful) contains potassium chloride 1.5 Gm., supplying 20 mEq. of elemental potassium, in a cherry-flavored, palatable base, alcohol 4%. Contains no sugar.
INDICATIONS: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium or as a result of excessive vomiting and diarrhea.
CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
SIDE EFFECTS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
DOSAGE AND ADMINISTRATION: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
HOW SUPPLIED: One pint and one gallon bottles.

Cooper Laboratories, Inc., Wayne, N.J. 07470/Ste. Therese, P.Q., Canada

FEBRUARY 1974

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Natural History of Angina Pectoris

Diagnostic Value of Echocardiography

Myocardial Infarction After Bypass Surgery

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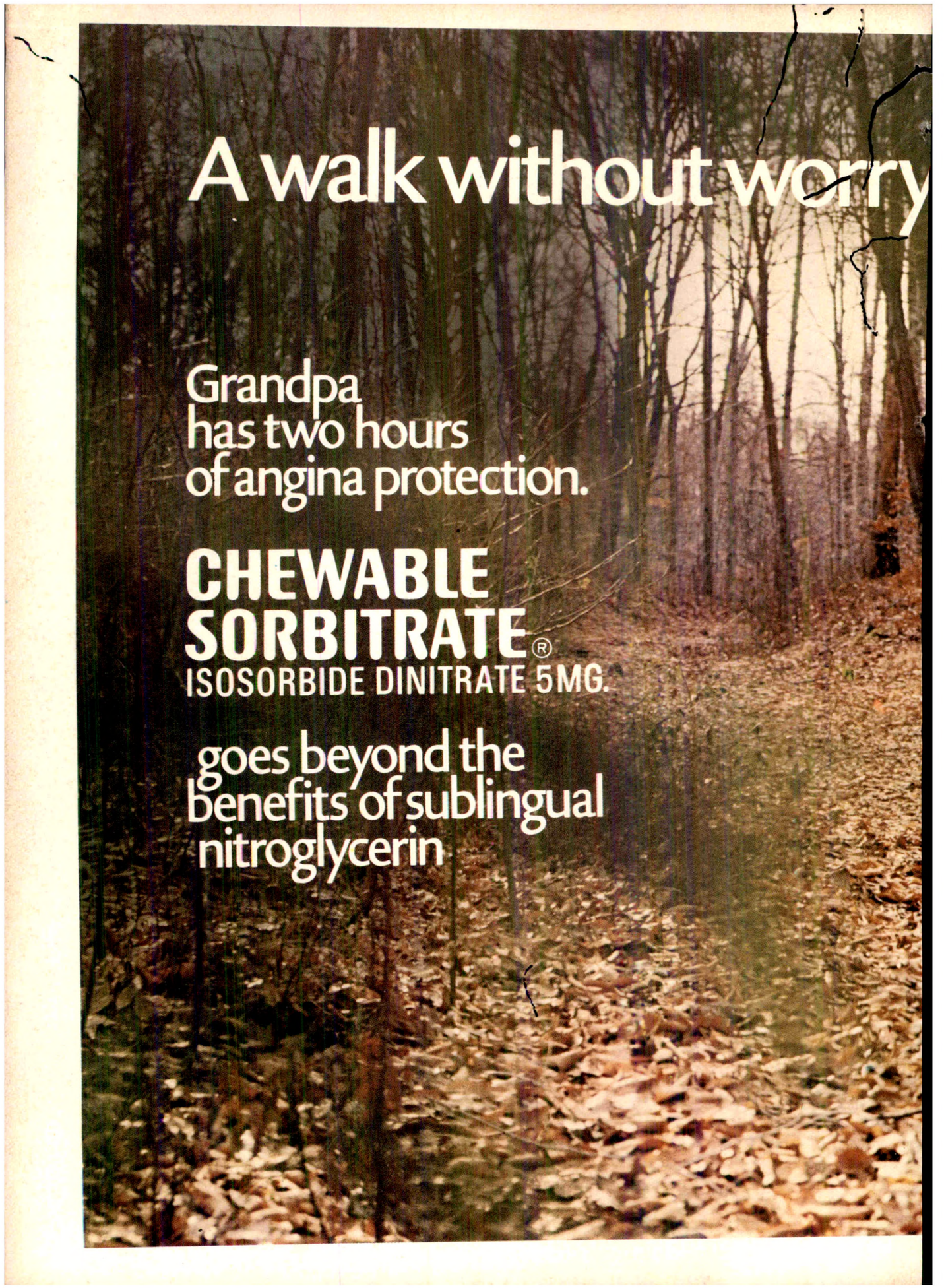
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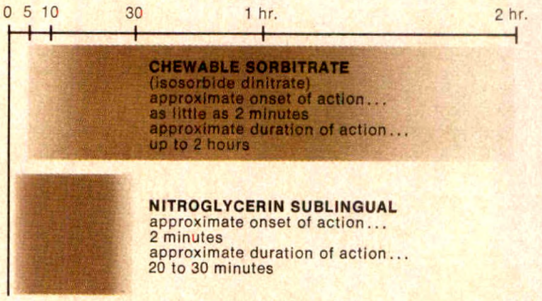
has two hours
of angina protection.
CHEWABLE
SORBITRATE®
ISOSORBIDE DINITRATE 5MG.
goes beyond the
benefits of sublingual
nitroglycerin

For up to two hours of protection, your angina patient needs *more* than sublingual nitroglycerin. And Chewable Sorbitrate provides more.

☐ Acts almost as fast as nitroglycerin...lasts about 4 times as long.



☐ More stable in air than sublingual nitroglycerin: it can be stored or carried with no significant loss of potency.

☐ And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS | Div of ICI America Inc.
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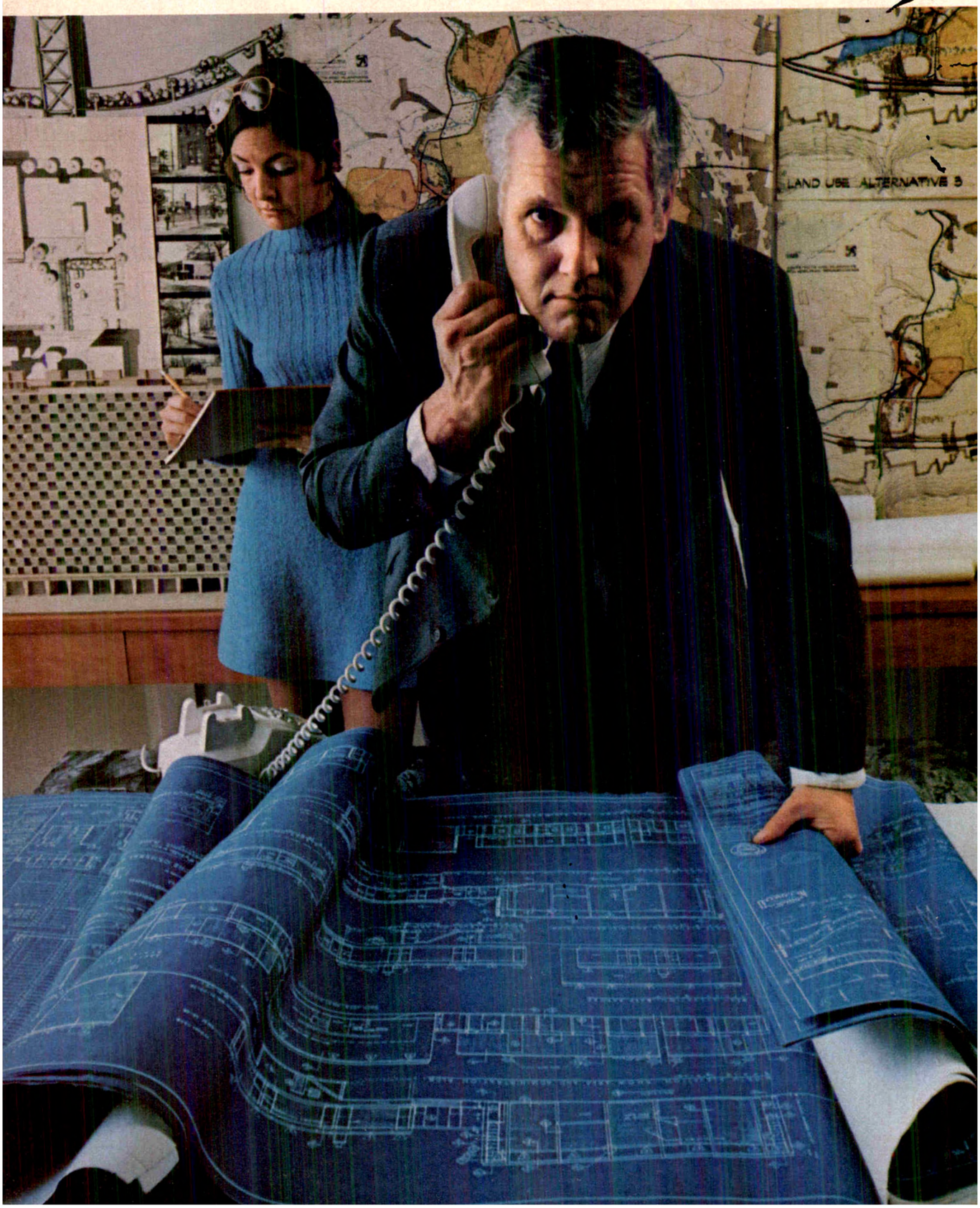
HE HAS THE DRIVE OF A FULLBACK— BUT THE BLOOD PRESSURE OF AN EARLY HYPERTENSIVE



IS HE A "POTASSIUM WASTER" AS WELL?

Bartels et al.[1] found that 28 of 65 hypertensive patients treated with chlorothiazide developed hypokalemia despite, in 12 cases, the concurrent administration of 2 or 3 grams of KCl daily. In 10 patients, hypokalemia persisted for up to 10 weeks in spite of remedial measures. They concluded: **"The long-term use of drugs which may cause potassium depletion must be carefully considered in these patients who may be potential potassium wasters."**

Hypokalemia is usually associated with a considerable reduction of total body potassium.[2] By prescribing 'Dyazide', you can protect patients against hypokalemia, because 'Dyazide' contains DYRENIUM® (brand of triamterene), the unique potassium-sparing agent which acts *independently* of aldosterone secretion. Thus, 'Dyrenium' works from the *first dose* and throughout therapy at constant dosage levels. And the combination in 'Dyazide' lowers blood pressure as effectively as plain thiazides.

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

The Dyrenium (triamterene, SK&F) component of 'Dyazide' conserves potassium. Therefore, dietary potassium supplements or potassium salts should not be used with 'Dyazide' unless hypokalemia develops or dietary intake of potassium is markedly impaired.

'Dyazide' can occasionally cause hyperkalemia. Accordingly, serum potassium and BUN should be checked during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetic patients). If hyperkalemia develops, 'Dyazide' should be withdrawn and a thiazide alone substituted.

Use 'Dyazide' with caution during pregnancy or in women who might bear children. Its potential benefits should be weighed against possible hazards to the fetus.

See next page for indications and brief prescribing information.

1. Bartels, C. C., et al.: Chlorothiazide—A Survey of Its Effects in Hypertensive Patients, J.A.M.A. 170:1796 (Aug. 8) 1959.

2. Edmonds, C.J., and Jasani, B.: Total-Body Potassium in Hypertensive Patients During Prolonged Diuretic Therapy, Lancet 2:8 (July 1) 1972.

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

TO BRING BLOOD PRESSURE DOWN TO KEEP POTASSIUM LEVELS UP

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules.

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THE AMERICAN JOURNAL OF CARDIOLOGY,® Official Journal of the American College of Cardiology, February, 1974, Vol 33, No. 2.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except September, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group, William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES: 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

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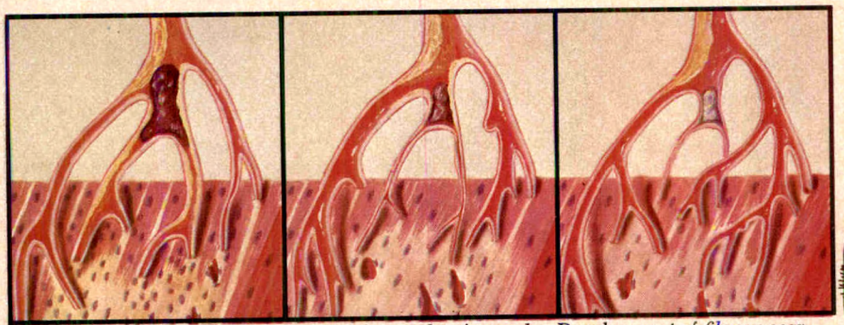
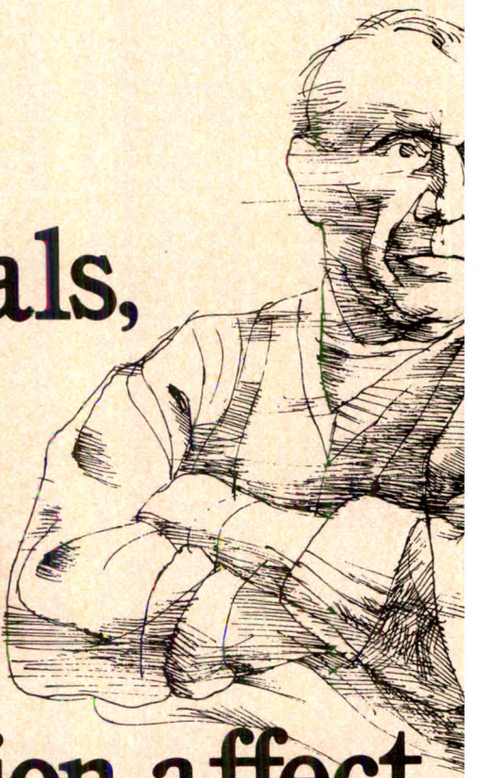
As the infarct heals,



Occlusion of vessel and acute infarct of the myocardium.

Damaged area showing early collateral vessel formation.

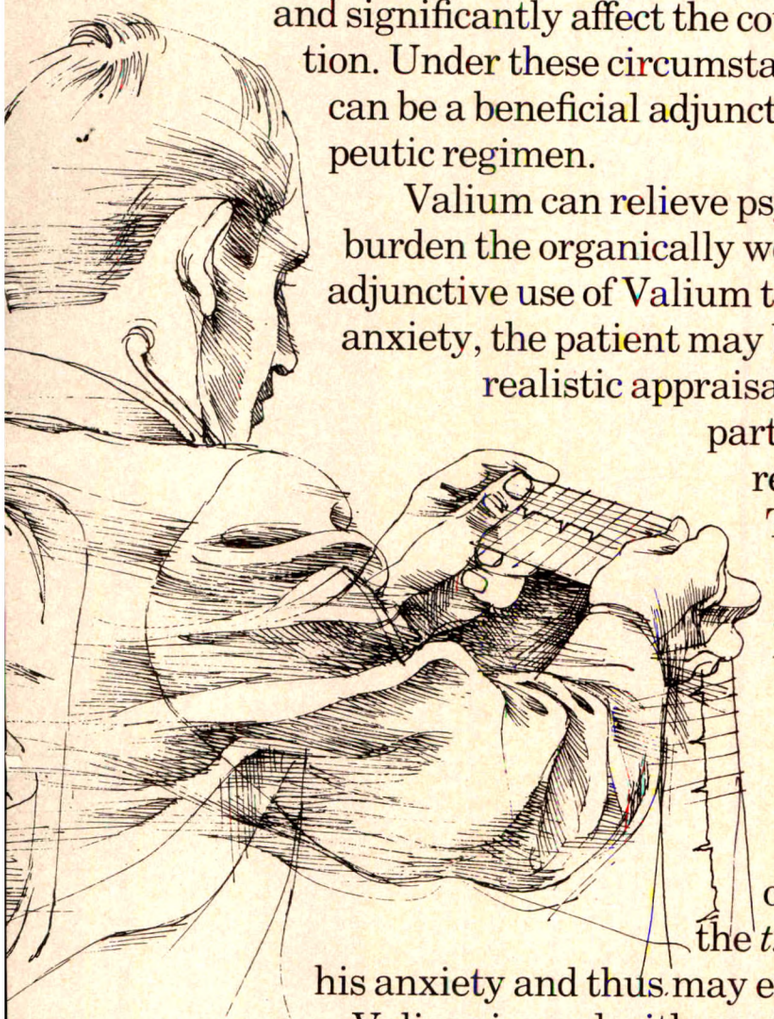
Development of fibrous scar and healing of infarcted area.



will psychic tension affect the patient's rehabilitation?

ROCHE

After the MI patient's acute episode has been successfully managed, a program of rehabilitation is begun. At times the overly tense cardiac patient may present a special problem. Although you continue to encourage a positive outlook through counseling and enlistment of support from the patient's family, psychic tension may remain, and significantly affect the course of rehabilitation. Under these circumstances, Valium (diazepam) can be a beneficial adjunct to the patient's therapeutic regimen.



Valium can relieve psychic tension that may burden the organically weak heart. As a result of adjunctive use of Valium to relieve unwarranted anxiety, the patient may be able to arrive at a more realistic appraisal of his situation and participate more fully with his rehabilitation program. Therapy should normally be continued until the patient's anxiety has been reduced to tolerable levels.

Since the cardiac patient may be particularly prone to tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *t.i.d.* schedule can relieve his anxiety and thus may encourage sleep.

Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticholinergics and antacids. The most commonly reported side effects have been drowsiness, fatigue and ataxia. Patients taking Valium should be cautioned against driving or operating dangerous machinery.

Valium®(diazepam)
2-mg, 5-mg, 10-mg tablets

when you consider it essential to keep the heart patient calm

Please turn page for a summary of product information.

When you consider it essential to keep the heart patient calm

- Valium (diazepam) can relieve psychic tension and anxiety that may burden the organically weak heart and interfere with the patient's course of rehabilitation.
- Valium works promptly in most patients. Significant improvement is usually noted during the first few days of therapy, although some patients may require more time to respond.
- Adjustments in dosage can alter clinical response. With appropriate titration, a regimen can be tailored to the patient's individual needs.
- Valium has a wide margin of safety in the usual oral dosage range and generally does not significantly affect respiration or pulse.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 1000.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

The American Journal of CARDIOLOGY®

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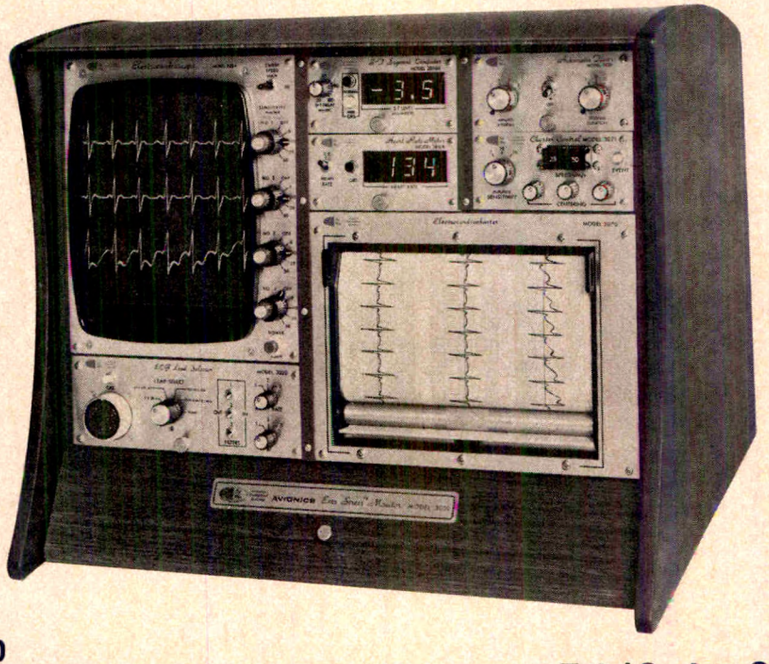

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195 **Natural History of Severe Proximal Coronary Artery Disease as Documented by Coronary Cineangiography**

JOEL S. WEBSTER, CARL MOBERG and GUSTAVO RINCON

Average yearly mortality rates in 469 patients with 80 to 100 percent occlusive lesions in the proximal coronary tree diagnosed by selective angiography were 4 percent in patients with isolated disease of the left anterior descending artery and 2.3 percent in those with isolated disease of the right coronary artery. Patients with double and triple vessel disease had, respectively, 41.5 and 63 percent 6 year mortality rates. Survival appeared to be related to the number of vessels involved. Patients with severe cardiomegaly, heart failure or left ventricular dysfunction were excluded from the study.

201 **Unstable Angina—Prospective and Randomized Study of Its Evolution, With and Without Surgery. Preliminary Report.**

CARLOS A. BERTOLASI, JORGE E. TRONGÉ, CÉSAR A. CARRENO, JORGE JALON and MARCELO RUDA VEGA

Unstable angina includes three major categories: (1) intermediate syndrome, (2) progressive angina, and (3) postinfarction angina. In this prospective and randomized study of 142 patients with unstable angina, the natural history of the patients in each group differed. Patients with an intermediate syndrome treated surgically had a significantly reduced mortality and the survivors were clinically better than medically treated subjects.

209 **Right Ventricular Infarction. Clinical and Hemodynamic Features**

JAY N. COHN, NABIL H. GUIHA, MARTIN I. BRODER and CONSTANTINOS J. LIMAS

The diagnosis of right ventricular infarction should be considered in any patient with an acute diaphragmatic wall infarction and evidence of systemic venous engorgement. Six such patients with hemodynamic evidence of right ventricular failure disproportionate to left ventricular failure, an unusual finding in patients with acute myocardial infarction, are described. Shock in three patients was successfully treated by plasma volume expansion to increase right-sided pressure or by the administration of sodium nitroprusside to reduce left-sided filling pressure.

215 **Electrocardiographic and Serum Enzyme Changes of Myocardial Infarction After Coronary Artery Bypass Surgery**

MALCOLM R. ROSE, EPHRAIM GLASSMAN, O. WAYNE ISOM and FRANK C. SPENCER

Postoperative myocardial infarction (new Q waves) occurred in 10 percent of 50 patients after coronary artery bypass surgery, in 20 percent of 15 patients after aortic valve replacement, and in none of 12 patients after mitral valve surgery. Myocardial infarction after coronary artery bypass surgery is more likely in patients with at least three vessel disease, but appears to be unrelated to pump time or aortic cross-clamping. Serum enzyme values correlated well with electrocardiographic evidence of infarction.

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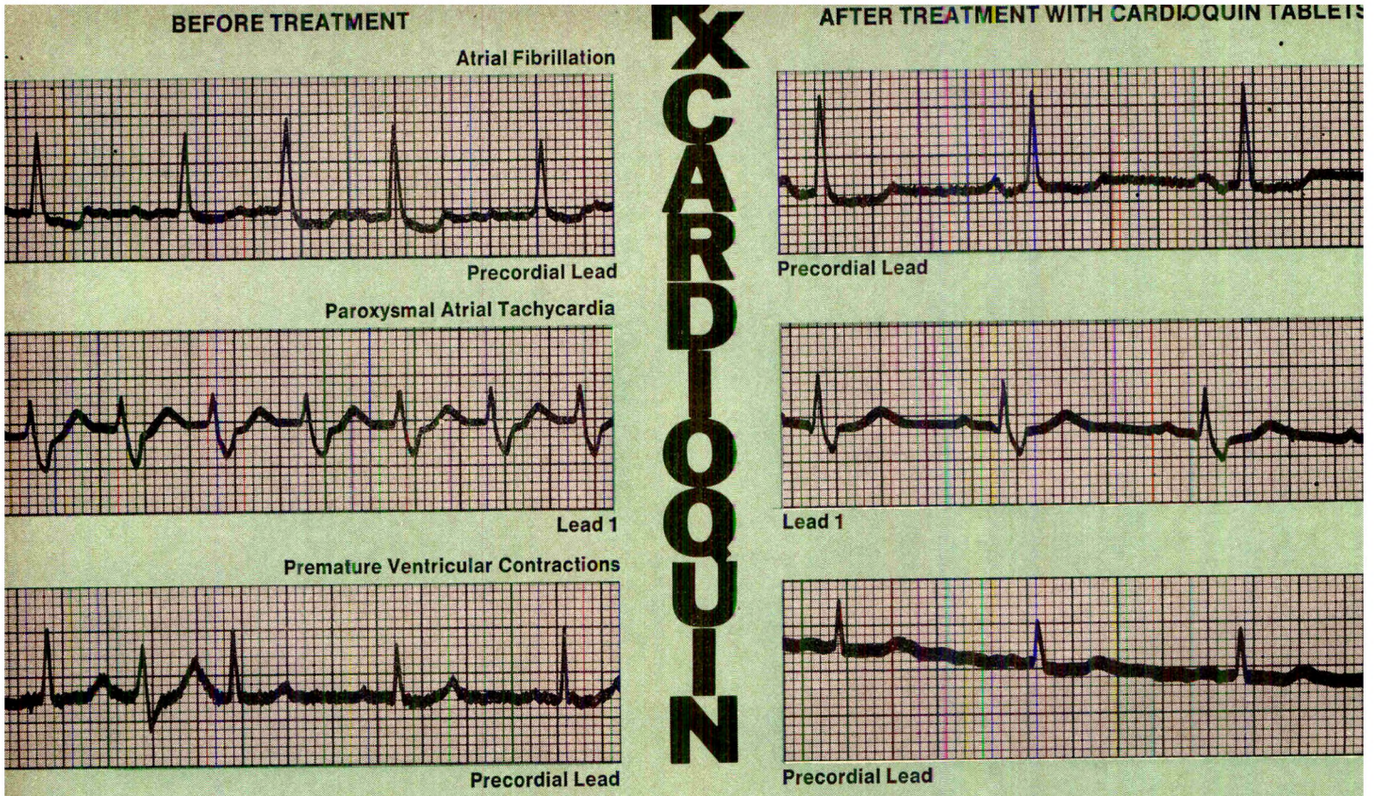

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221 New Q Waves After Coronary Artery Bypass Surgery for Angina Pectoris

JAIME ESPINOZA, JANET LIPSKI, ROBERT LITWAK, EPHRAIM DONOSO and SIMON DACK

Postoperative electrocardiograms in 44 patients with angina pectoris who underwent single or multiple coronary artery bypass procedures and, in 7 cases, additional surgery demonstrated new Q waves in 30 percent of the patients who underwent bypass procedures alone. The prevalence of new Q waves was greater in those who had two or three vessel disease demonstrated by coronary arteriography before operation and in those who had three coronary bypasses. The postoperative clinical course and mortality rates were not affected.

225 Correlation of Serum Magnesium Levels and Cardiac Digitalis Intoxication

GEORGE A. BELLER, WILLIAM B. HOOD, Jr., THOMAS W. SMITH, WALTER H. ABELMANN and WARREN E. C. WACKER

Hypomagnesemia occurred in 21 percent of patients with and 10 percent of those without digitalis toxicity. Hypermagnesemia was significantly greater in patients with digitalis toxicity (18 percent) than in those without toxicity (5 percent), probably the result of the greater prevalence of abnormal renal function in the former group. Further investigation of the value of giving magnesium to hypomagnesemic patients with digitalis toxicity is indicated.

230 Influence of Exercise on Arrhythmias Induced by Digitalis-Diuretic Therapy in Patients with Atrial Fibrillation

ALDEN S. GOOCH, GANGAIAH NATARAJAN and HARRY GOLDBERG

In 20 ambulatory patients with atrial fibrillation low-level treadmill exercise testing provided a simple method of provoking latent cardiac irritability in patients with suspected digitalis and diuretic toxicity. Arrhythmias suggesting digitalis toxicity were junctional tachycardia with or without exit block, frequent ventricular beats and bigeminy. Serial exercise testing after withdrawal of the drugs demonstrated devolution of the arrhythmias.

EXPERIMENTAL STUDIES

238 Effect of Procainamide on Fibrillation Threshold of Normal and Ischemic Ventricles

MYUNG S. YOON, JAOK HAN, BRIJ G. GOEL and PAULA CREAMER

In these dog experiments procainamide at therapeutic blood levels increased the mean fibrillation threshold 88 percent in normal ventricles and only 63 percent in dogs with acute coronary occlusion. Procainamide did not completely revert the decreased fibrillation threshold to normal values during acute myocardial ischemia, thus indicating that it is inferior to lidocaine in reducing the vulnerability of the ischemic myocardium to ventricular fibrillation.

243 Ventricular Defibrillation in the Dog Using Implanted and Partially Implanted Electrode Systems

JOHN C. SCHUDER, HARRY STOECKLE, JERRY H. GOLD, JOE A. WEST and JAMES A. HOLLAND

Ventricular defibrillation in large anesthetized dogs can be better achieved at any given percent success level with significantly less energy in systems involving a right atrium-superior vena cava electrode (catheter-internal disk or catheter-external disk systems).

Continued on page A-15

situation:

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248 **Accelerated Cardiac Escape Rhythms Caused by Ouabain Intoxication**

DOUGLAS P. ZIPES, EMANUEL ARBEL, RUSSEL F. KNOPE and GORDON K. MOE

Ectopic activity associated with early ouabain toxicity in anesthetized dogs appears to be caused by frequency-related transient depolarizations rather than "true" phase 4 depolarization or reentry.

254 **Predominant Right Ventricular Dysfunction After Right Ventricular Destruction in the Dog**

NABIL H. GUIHA, CONSTANTINOS J. LIMAS and JAY N. COHN

Damage of the right ventricle in dogs produces predominant right ventricular dysfunction but does not precipitate profound dysfunction with a low output state so long as intravascular volume is adequately expanded and pulmonary vascular resistance is not increased. An increase in cardiac output can be attained either by volume expansion or by reduction in left atrial pressure.

METHODS

259 **Complications of Percutaneous Femoral Arterial Catheterization. Prospective Evaluation with the Doppler Ultrasonic Velocity Detector**

ROBERT W. BARNES, JOHN L. PETERSEN, RICHARD B. KRUGMIRE, Jr. and D. EUGENE STRANDNESS, Jr.

The rate of complications was 14 percent in 160 percutaneous femoral arterial catheterizations in 142 adult patients at two hospitals. These complications included one accidental dissection of the iliac artery and 22 arterial thromboemboli. The location of thromboemboli was related to the duration of use of an indwelling arterial catheter. The use of a Doppler ultrasonic velocity detector before and after each procedure proved simple, rapid and effective for assessing limb hemodynamics.

264 **New Instrument for Transvenous Cardiac Biopsy**

PHILIP K. CAVES, WERNER P. SCHULZ, EUGENE DONG, Jr., EDWARD B. STINSON and NORMAN E. SHUMWAY

With newly developed forceps serial percutaneous transvenous endomyocardial biopsies have been routinely performed in new heart transplant recipients and in patients with primary cardiomyopathy. One hundred and sixty-three biopsy specimens have been obtained from 19 transplanted human hearts during 85 biopsy procedures.

HISTORICAL MILESTONES

268 **Julius Cohnheim's Experiments on Heart Valves**

SAUL JARCHO

Julius Cohnheim, one of the geniuses of experimental pathology in the last century and a teacher of William Welch, greatly influenced American pathology. These excerpts present his observations on experimentally produced valvular disorders.

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PROGRESS REPORTS

271 Principles and Pitfalls in Establishing Normal Electrocardiographic Limits

ERNST SIMONSON

Three main prerequisites for establishing valid normal electrocardiographic limits include (1) adequate sample size, (2) a sample representative of the average healthy population, and (3) adequate statistical evaluation. Many studies of normal electrocardiographic values fall short of these standards, particularly that for adequate sample size.

DIAGNOSTIC SHELF

277 Echocardiographic Manifestations of Discrete Subaortic Stenosis

RICHARD H. DAVIS, HARVEY FEIGENBAUM, SONIA CHANG, LEE L. KONECKE and JAMES C. DILLON

Echocardiographic patterns suggestive, if not specific, for discrete membranous subaortic stenosis as found in three verified cases include: early systolic closure of aortic valve, persistent valve closure throughout the remainder of systole, coarse fluttering of the leaflets, and absence of asymmetric septal hypertrophy.

281 Echocardiographic Diagnosis of Left Atrial Myxoma

ENRIQUE C. MARTINEZ, THOMAS D. GILES and GEORGE E. BURCH

Echocardiography easily led to the correct diagnosis and ruled out mitral stenosis in a patient in whom cardiac catheterization missed the presence of left atrial myxoma. The motion of the tumor produces a characteristic wavy appearance of interrupted echo traces representing echoes from the tumor mass. The echocardiogram is extremely useful in diagnosing obstructive lesions of the mitral valve orifice.

286 Delayed Systolic Peak of the Femoral Pulse from Kinking of the Aortic Arch

KYUHYUN WANG, DONALD HARRINGTON and FREDARICK L. GOBEL

Indirect pulse tracings taken simultaneously from the femoral and the right radial arteries revealed a delayed femoral pulse due to a longer systolic build-up time in the femoral artery than in the radial artery. This finding led to the diagnosis of kinking of the aortic arch in an asymptomatic 38 year old man.

CASE REPORTS

291 Demonstration of Dual Atrioventricular Nodal Pathways in Man

KENNETH M. ROSEN, ASHWIN MEHTA and ROBERT A. MILLER

The demonstration of two ranges of A–H intervals as well as dual atrioventricular nodal effective and functional refractory periods in a child after repair of a ventricular septal defect provides supporting evidence for the presence of dual atrioventricular nodal pathways.

Continued on page A-19

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Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

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Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

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Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

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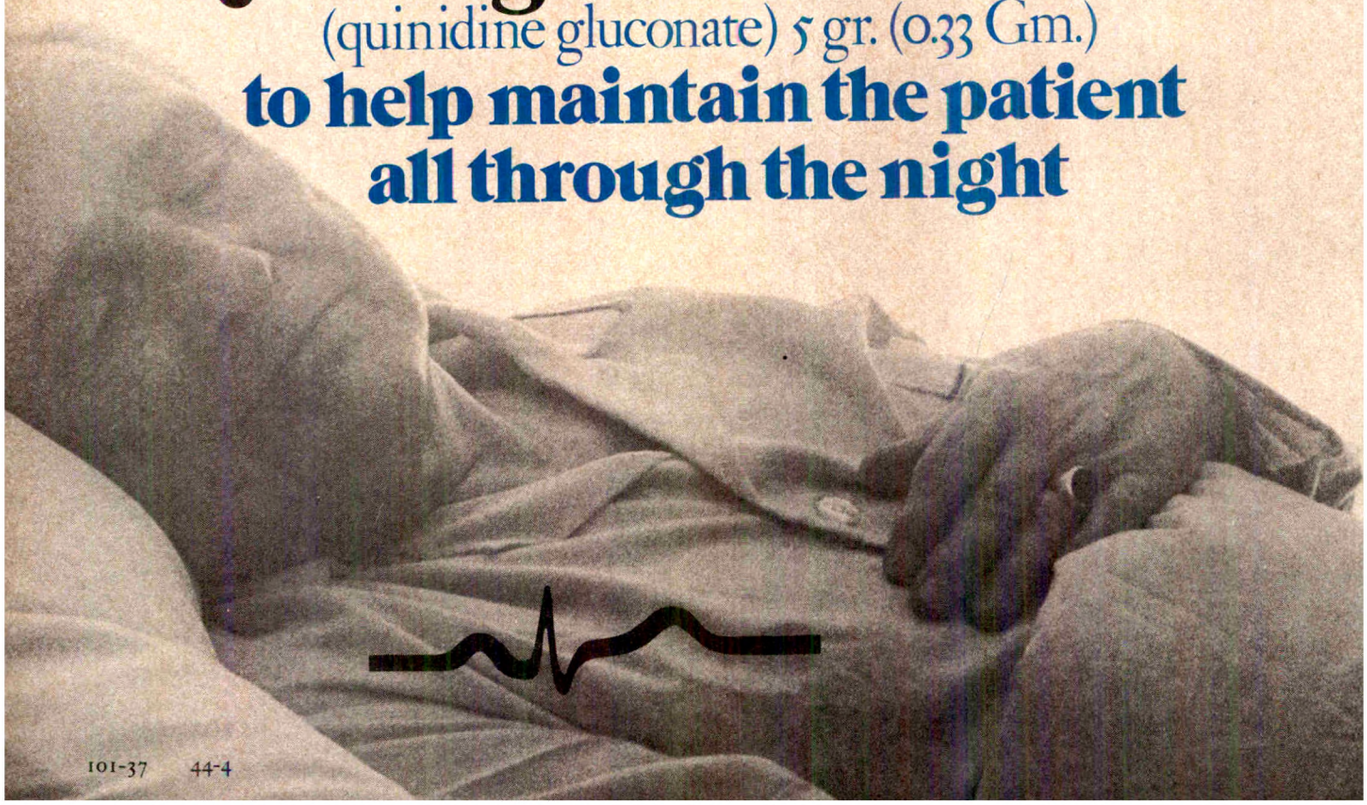

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295 **Pacemaker-Induced Cardiovascular Failure. Hemodynamic and Angiographic Observations**

JOHN M. HAAS and GAIL B. STRAIT

Severe acúte mitral regurgitation with decreased effective stroke volume and cardiac output as a result of loss of atrial contribution to ventricular filling and stroke volume were documented in a 71 year old woman after implantation of a permanent transvenous right ventricular pacemaker. These detrimental effects necessitated removal of the pacemaker.

300 **Double Opening Sound Related to Dysfunction in a Caged Disc Mitral Valve Prosthesis**

EARL C. HARRISON, E. JOHN ROSCHKE, MASAYOSHI MATSUNO and JOHN W. ALLEN

This case report illustrates the value of phonocardiography in detecting the dysfunction of mitral caged disc prostheses. An extra opening click present before embolization disappeared coincidentally with the occlusion of the left femoral artery by a grooved embolic fragment presumed to arise from the Kay-Shiley caged disc mitral valve prosthesis.

304 **Multiple Coronary Arteriosystemic Fistulas**

KOTA REDDY, MOHINDER GUPTA and ROBERT I. HAMBY

In a 58 year old man with angina pectoris and no heart murmur, selective coronary angiography disclosed multiple coronary arteriosystemic fistulas involving all three major coronary arteries which communicated through Thebesian vessels with the left ventricle. The normal pulse pressure and absence of left ventricular hypertrophy suggest that there was no hemodynamically significant volume overload on the left ventricle.

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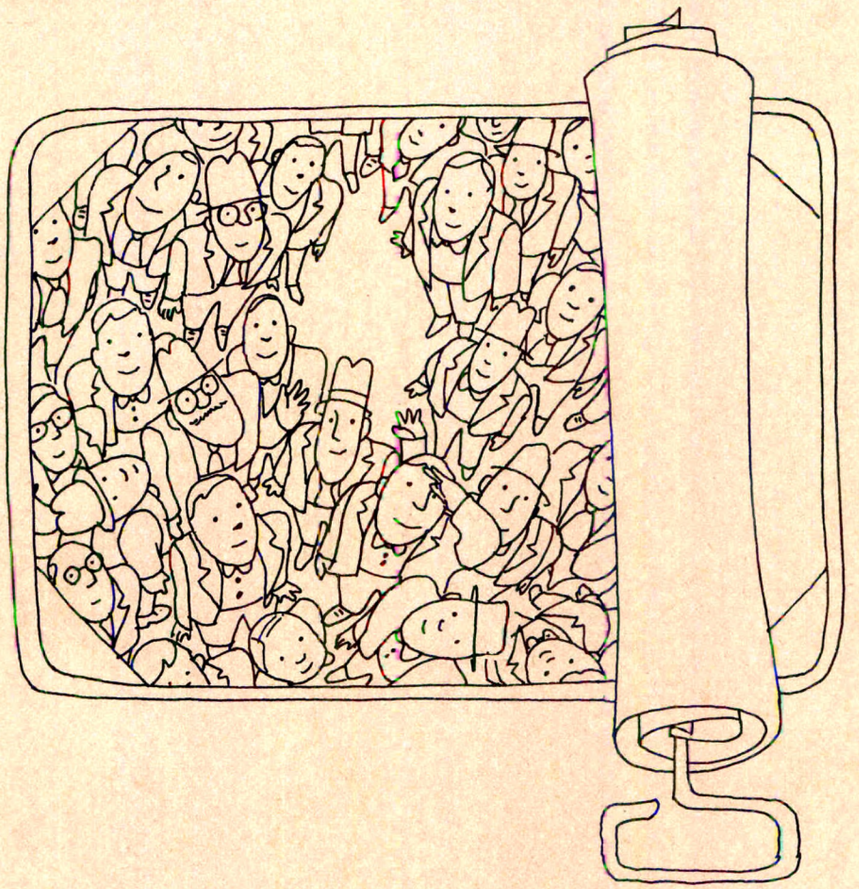

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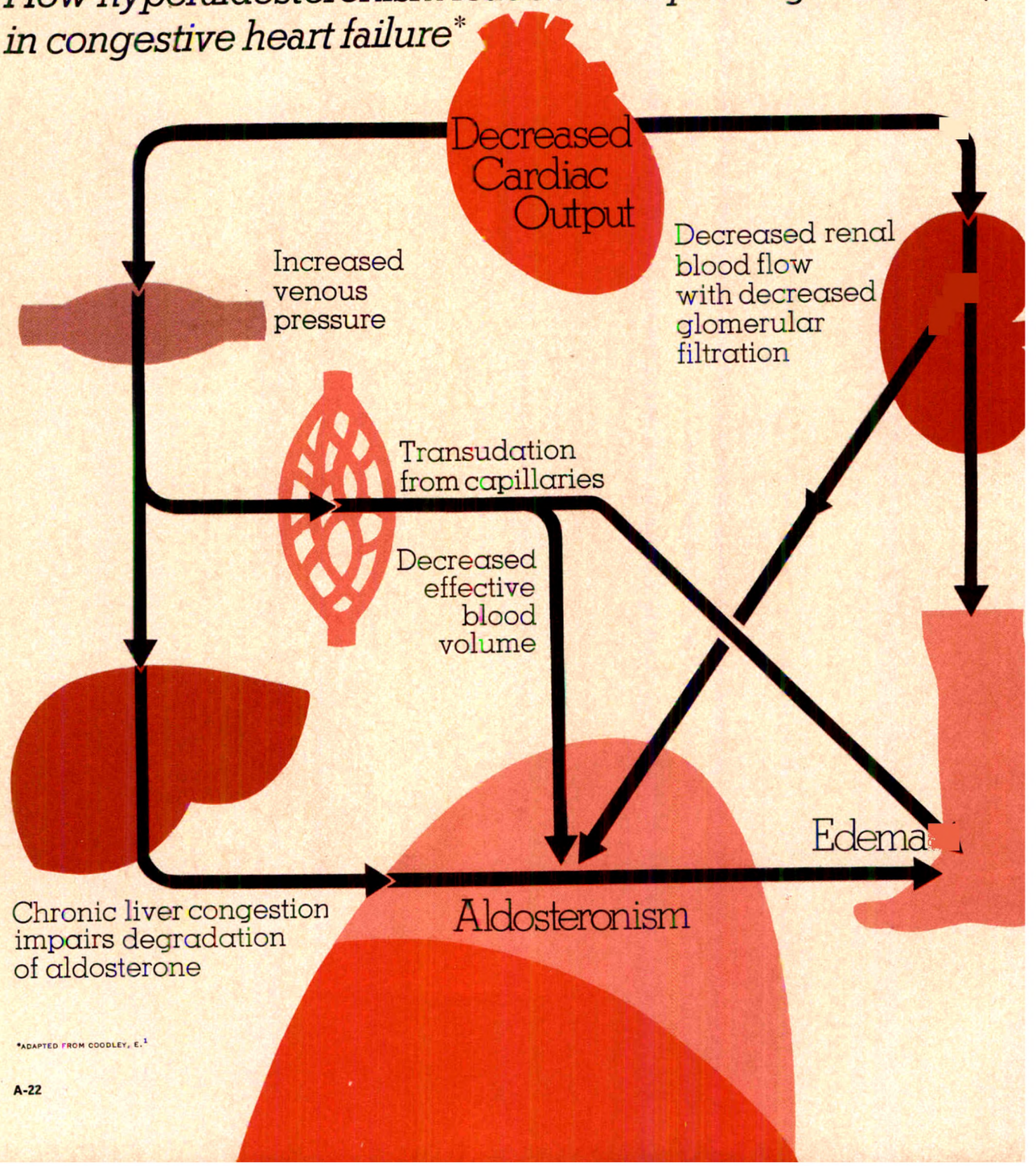

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- Can be administered daily as basic therapy with the additional agent (furosemide or ethacrynic acid) given every second or third day.
- Aldactone plus "A.D.D." schedule minimizes potassium deficiency and potentiates effect of "add-on" diuretic.[2]
- Avoids acute volume depletion and aldosterone rebound.[2]

3. As a daily diuretic in combination with a daily dose of a thiazide

- Permits daily additive diuretic effect while maintaining potassium balance.

Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone (spironolactone), particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For **essential hypertension** in **adults** the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema, ascites or **effusions** in **adults** initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For **children** the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References: 1. Coodley, E.: Consultant 12:106-107, 109, 111, 113, 115 (July) 1972. **2.** Thorn, G. W., and Lauler, D. P.: Am. J. Med. 53:673-684 (Nov.) 1972.

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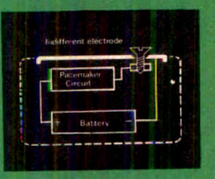

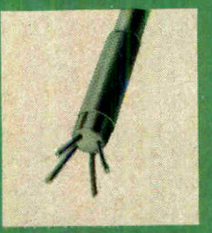

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Other important features contributing to the longevity and reliability of Vitatron Medical's new generation of fully analysable pacemakers are

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The Four Horsemen of Stroke...

HYPERTENSION

HEART DISEASE

DIABETES

ELEVATED CHOLESTEROL

You have your own therapeutic regimen to reduce these risk factors—the "Big Four" accelerators of stroke.

...and TIA's-the Prophetic Fifth Horseman

Transient Ischemic Attacks (TIA's) are another signal of impending stroke that is particularly ominous. In fact, 33% of patients with TIA's will develop a severe neurological deficit within 5 years.*

For such patients, PAVABID® (papaverine HCl) vasodilatation helps to preserve cerebral circulation. By reducing arterial tone, Pavabid therapy helps block vasospasm that can result in neurological damage.

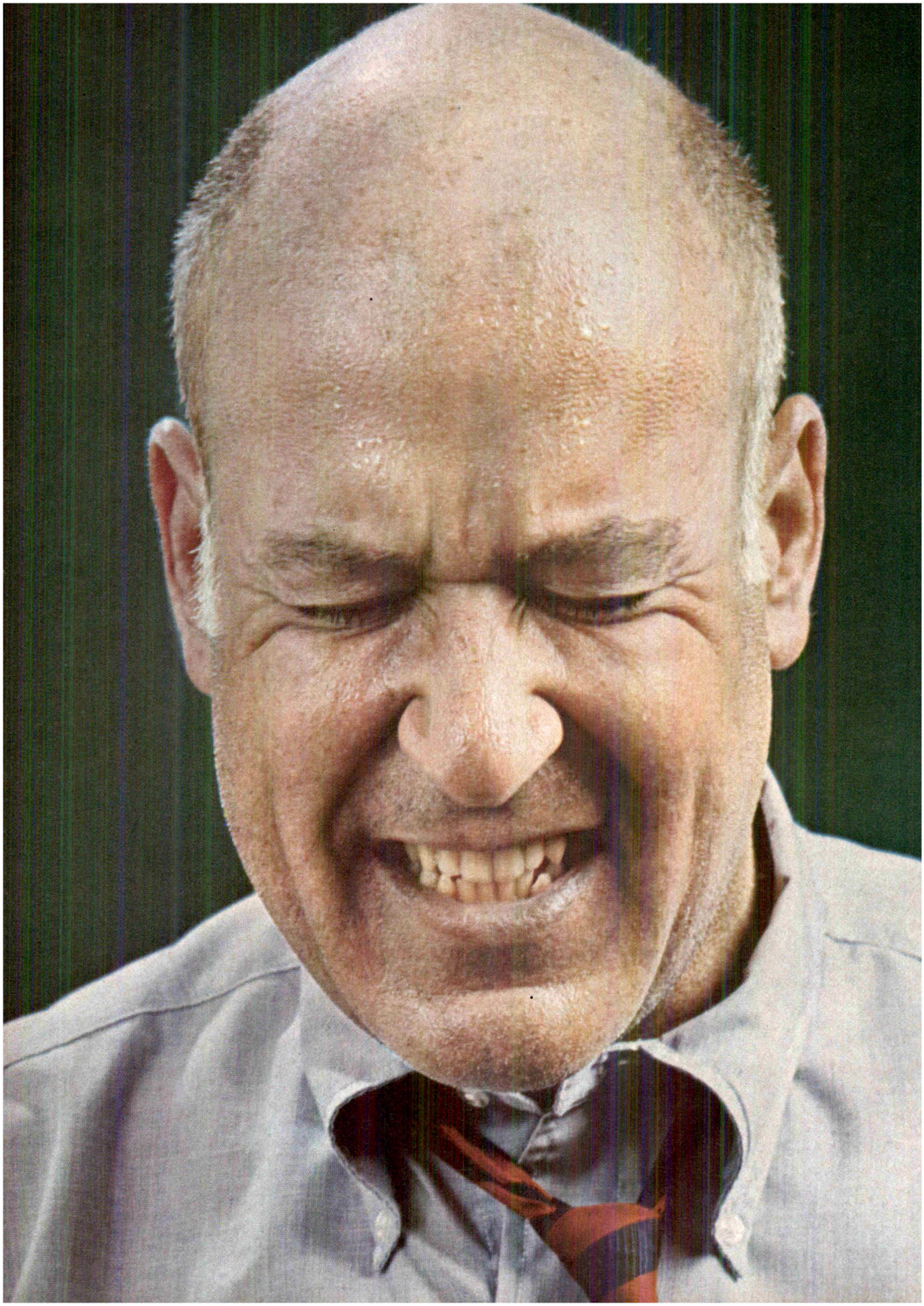
*Meyer, J. S., and Gilroy, J.: *Medical Neurology*

PAVABID®
(papaverine HCl, 150 mg.) Plateau CAPS®

Pavabid® Plateau CAPS® (Papaverine HCl, 150 mg.)—Each capsule contains papaverine hydrochloride, 150 mg. in a special base for prolonged therapeutic effect. *Indications:* ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias. *Dosage:* One capsule every 12 hours. In difficult cases, administration may be increased to one capsule every 8 hours, or two capsules every 12 hours. *Precaution:* Use with caution in patients with glaucoma. Hepatic hypersensitivity has been reported with gastrointestinal symptoms, jaundice, eosinophilia and altered liver function tests. Discontinue medication if these occur. *Side effects:* Infrequently reported side effects of papaverine include nausea, abdominal distress, anorexia, constipation, malaise, drowsiness, vertigo, sweating and headache, diarrhea and skin rash.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION



A new approach in the management of angina pectoris...

Inderal®

Brand of

propranolol hydrochloride

For patients unresponsive to conventional measures

When conventional methods such as weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances prove to be inadequate, a new mechanism for the management of moderate to severe angina pectoris is provided by INDERAL—the first beta-adrenergic blocking agent in clinical cardiologic use. INDERAL should not be used in patients with angina which occurs only with considerable effort or with precipitating factors that occur infrequently.

Distinctive mode of action: works to decrease myocardial oxygen demand, prevent oxygen deficit in responsive patients

When physical or psychological stress increases beta-adrenergic stimulation of the heart, oxygen demand may exceed capacity for oxygen delivery in a coronary circulation compromised by atherosclerosis. The result is anginal pain.

INDERAL—through its beta-adrenergic blocking action—provides a unique approach. By specifically competing with catecholamines for available myocardial beta-receptor sites, INDERAL can reduce sympathetically induced increases in heart rate, systolic blood pressure and velocity of contraction during exercise or stress—and thus decrease the oxygen requirements of the heart. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to the decreased oxygen requirement.

Ayerst

USE OF INDERAL®/ANGINA PECTORIS CONTINUED ON NEXT PAGE

(See last two pages of advertisement for prescribing information.)

Inderal®
(propranolol hydrochloride)
for moderate to severe angina pectoris

Wide clinical experience

The use of INDERAL (propranolol hydrochloride) in angina pectoris has been the subject of numerous published papers, including 33 on controlled clinical trials (28 double-blind) involving 746 patients,[1-33] and 27 on other studies covering 774 patients. The results of these studies support INDERAL's usefulness in reducing incidence of pain and increasing exercise tolerance in patients with angina pectoris. Proof of effectiveness has been demonstrated both *clinically* and by *objective laboratory measurements*.[1-29,31-33]

Decrease in frequency of anginal attacks and reduced need for nitroglycerin shown in controlled clinical studies

Thirty of the above papers reported on the effect of INDERAL on incidence of anginal pain and consumption of nitroglycerin. INDERAL was found to be effective in reducing the incidence of anginal pain and the consumption of nitroglycerin in 29 of these 30 controlled clinical trials.[1-29] Of the 29 studies reporting effectiveness with INDERAL, results were deemed statistically significant in 19,[1-19] not statistically significant in 2,[20,21] and the statistical significance was not given in 8 studies.[22-29] One study[30] reported that propranolol was not effective.

In 24† of these clinical studies, it was possible to determine the proportion of patients responding to treatment. The results showed that approximately three-quarters of the patients had less pain and used less nitroglycerin when taking INDERAL than on placebo.

Improvement in exercise tolerance demonstrated by objective laboratory measurements

Seventeen of the controlled trials dealt with the effect of oral INDERAL on exercise tolerance. Of these, INDERAL was found to be effective in 14,[2,8,10,12,13,15,16,18,22,23,25,27,28,32] and not effective in three.[3,29,30] Of the fourteen studies reporting effectiveness with INDERAL, the improvement was statistically significant in eight,[2,8,10,12,15,16,18,32] and significance was not given in six.[13,22,23,25,27,28]

For example in a double-blind study, the effect of INDERAL (propranolol hydrochloride) on exercise tolerance was examined by Gianelly and associates. In a double-blind crossover study of 19 patients, the effects of INDERAL on exercise tolerance were assessed and correlated with cardiovascular physiologic effects.[8] Nineteen patients (18 male and 1 female) with a typical history of angina and a positive Master test, ranging in age from 38 to 65 years, received for 4 weeks either placebo or 160 mg. INDERAL daily in 4 divided doses. During the study, exercise tolerance was assessed using a treadmill which was adjusted for speed and incline so that each patient would experience chest pain within one to five minutes. Measurements were made at the end point of each test (pain, fatigue, or dyspnea). From this study and a subsequent study,[31] the investigators concluded that in responsive patients INDERAL, by reducing cardiac work, tends to bring into balance myocardial oxygen supply and need, and increases exercise tolerance.

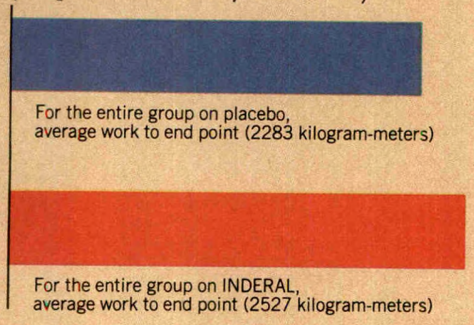
Side effects, including bradycardia, nocturnal dyspnea, mildly blurred vision, diarrhea and postural hypotension, occurred in 5 patients, but did not require permanent discontinuation of the drug.

†1-9, 11-15, 17, 18, 20-24, 26, 27, 30

With 160 mg. INDERAL (propranolol hydrochloride) daily—increase in exercise tolerance with treadmill test (kilogram-meters)

160 mg. INDERAL daily increased exercise tolerance by 22% in 14 of 18 patients who completed exercise to an end point of pain, fatigue or dyspnea. For the total group, the average increase in exercise tolerance on INDERAL 160 mg. daily was 11%. Incomplete data on one patient reduced the number to 18 for this aspect of the study.

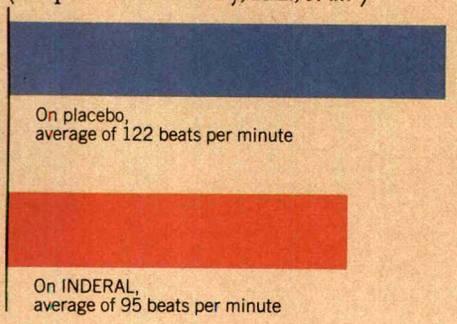
(Adapted from Gianelly, R.E., *et al.*[8])



With 160 mg. INDERAL daily—reduction of heart rate on exercise

160 mg. INDERAL daily reduced heart rate in all 19 subjects at end point of standard exercise procedure.

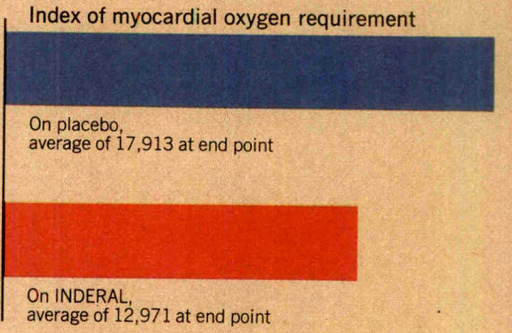
(Adapted from Gianelly, R.E., *et al.*[8])



With 160 mg. INDERAL (propranolol hydrochloride) daily—reduction of myocardial oxygen requirement on exercise (by the treadmill test)

Index of myocardial oxygen requirement at end of exercise, as measured by the product of systolic blood pressure and heart rate, "was consistently reduced by propranolol..." in 19 patients taking 160 mg. INDERAL daily.

(Adapted from Gianelly, R.E., *et al.*[8])



It is important that the dosage be titrated and individualized for maximum effect

Starting with 10-20 mg. 3 or 4 times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. Higher doses may be required; however, the value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, it is recommended that withdrawal be gradual over a two-week period. (See PRECAUTIONS.)

Special caution should be observed in patients with heart block or a history of congestive heart failure. (See CONTRAINDICATIONS AND WARNINGS.)

Good medical practice dictates that INDERAL should not be continued unless there is reduced pain or increased work capacity. Treatment should be carefully monitored.

INDERAL will not interfere with the cardiac action of sublingual nitroglycerin, or cardiotonic agents such as digitalis.

USE OF INDERAL®/ANGINA PECTORIS CONTINUED ON NEXT PAGE

Ayerst

(See last two pages of advertisement for prescribing information.)

Inderal®

(propranolol hydrochloride)

for moderate to severe angina pectoris in responsive patients

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®

Brand of

propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL (propranolol hydrochloride), the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support or vital functional balances.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias

associated with pheochromocytoma, thyrotoxicosis, exercise).

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end-diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: *Angina Pectoris Due to Coronary Atherosclerosis.* The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL (propranolol hydrochloride) is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL (propranolol hydrochloride) should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

In chronically treated patients, dosage should be gradually reduced over a two week period when it is anticipated that the administration of INDERAL will be discontinued. There have been a few reports of myocardial infarction occurring within 2-3 days of propranolol hydrochloride discontinuation in angina pectoris patients, but an association has not yet been established.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, non-thrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

Angina Pectoris—Dosage must be individualized. Starting with 10-20 mg. three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. The value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, it is recommended that withdrawal be gradual over a two week period. (See PRECAUTIONS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL®
(propranolol hydrochloride)

TABLETS

No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

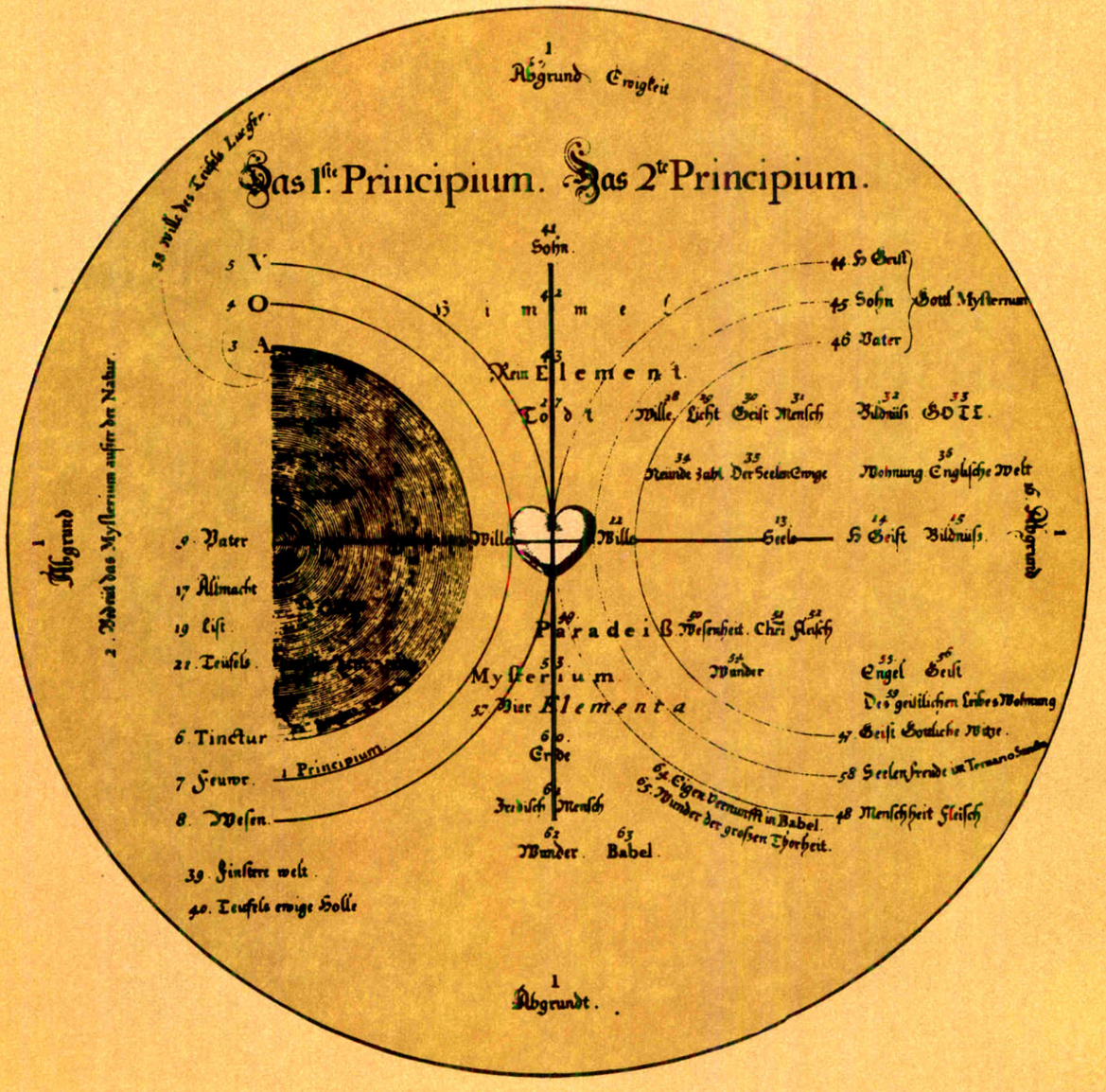
INJECTABLE

No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst. AYERST LABORATORIES
NEW YORK, N.Y. 10017

INDERAL® (propranolol hydrochloride) is available in the United States by arrangement with Imperial Chemical Industries Ltd. 7355

Die Philosophische Kugel oder das Wunder-Auge der Ewigkeit.



The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

Persantine — over a decade of use

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Persantine — give enough — long enough

The recommended dosage: 50 mg. t.i.d. at least one hour before meals. *Give enough, long enough* — several weeks or longer of continuous therapy may be needed to see response.

Persantine® Tablets of 25 mg.
dipyridamole

the non-nitrate
coronary vasodilator

*INDICATIONS – Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS – No specific contraindications are known.

PRECAUTIONS – Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS – Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION – The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

The Philosophical Sphere
The philosophical sphere, according to Jakob Böhme. The "true psychology" or forty questions about the soul (1620).

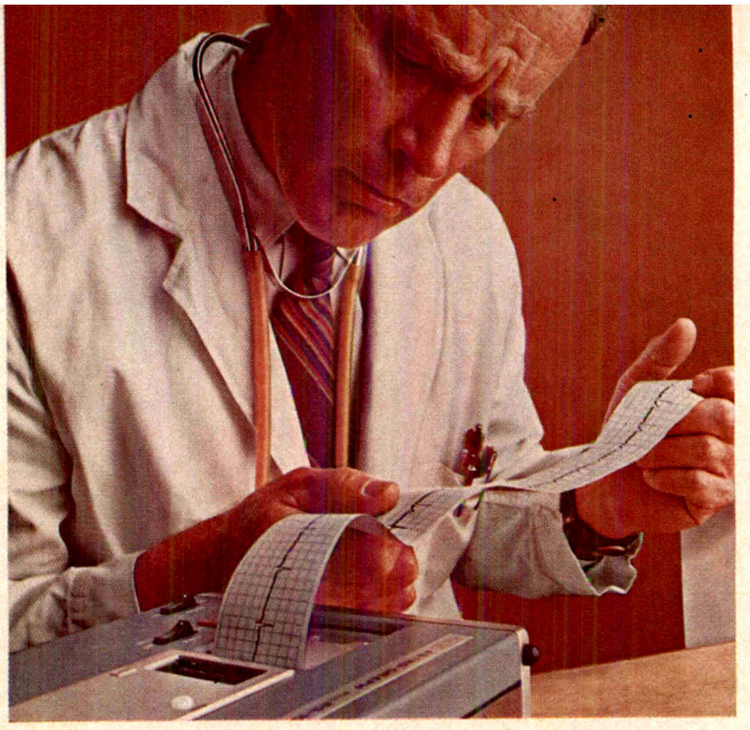
"The heart set in the angle of the cross means the basis or center of the Divinity . . . that we may learn to distinguish the Divinity from nature, and that Christians may learn to understand the rebirth, how God in Christ, out of his crucified heart, resurrected us."

BOEHRINGER INGELHEIM

Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

When cardiac complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on heart function

Excessive anxiety is one of a combination of factors that may trigger a series of maladaptive functional reactions which can generate further anxiety. Often involved in this vicious circle are some cardiac arrhythmias, paroxysmal supraventricular tachycardia and premature systoles. When these symptoms resemble those associated with actual organic disease, the overanxious patient needs reassurance that they have no

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

organic basis and that reduction of excessive anxiety and emotional overreaction would be medically beneficial.

The benefits of antianxiety therapy

Antianxiety medication, when used to complement counseling and reassurance, should be both effective and comparatively free from undesirable side effects. More than 13 years of extensive clinical experience has demonstrated that Librium (chlordiazepoxide HCl) fulfills these requirements with a high degree of consistency. Because of its wide margin of safety, Librium may generally be administered for extended periods, at the physician's discretion, without diminution of effect or need for increase in dosage. (See summary of prescribing information.) If cardiovascular drugs are necessary, Librium is used concomitantly whenever anxiety is a clinically significant factor. (See Precautions.) Librium should be discontinued when anxiety has been reduced to appropriate levels.

For relief of excessive anxiety adjunctive

Librium® 10 mg
(chlordiazepoxide HCl)
1 or 2 capsules t.i.d./q.i.d.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

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in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

ENERGY: How the new Medtronic

For complete product information, contact your local Medtronic Representative or Medtronic Corporate Headquarters:

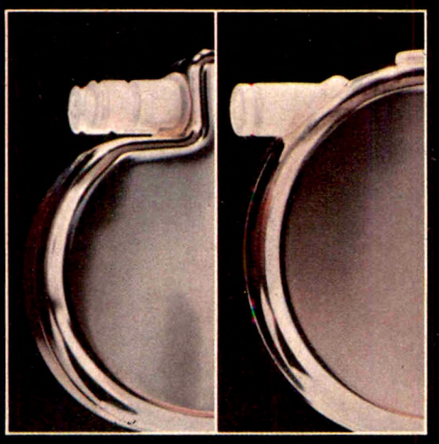
Medtronic, Inc.
3055 Old Highway Eight
Minneapolis, Minn. 55418
Telephone 612/781-6061

pacemakers conserve it.

The concept of Energy Conservation is based on one simple fact: lessen the drain on a power source and you extend its life.

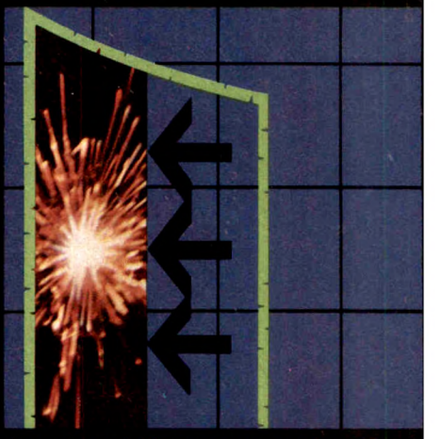
In the new Medtronic pacemakers, pulse width has been reduced to reduce the energy expenditure per pulse.

Less energy expended means longer projected life. It's that simple.



Model 5944—Bipolar Demand Pulse Generator

Model 5945—Unipolar Demand Pulse Generator



As pulse width narrows, projected life of the pulse generator is extended.

Another significant improvement combines the idea of energy compensation with a redundant cell depletion indicator. It works this way: when depletion of the first cell occurs, the new Medtronic pulse generators show a decrease in rate similar to most other pulse generators. But, they also automatically increase pulse width when depletion occurs. This increase in pulse width compensates for the decrease in voltage, thus providing a margin of safety above threshold while also serving as a positive cell depletion indicator.

By now she should

Rheumatic fever prevention and the noncompliant patient.

Patients on oral penicillin for prevention of recurrent rheumatic fever usually don't ignore their daily dosage regimen deliberately. But since patients are only human, doses *are* missed occasionally—through simple lapse of memory, lack of time or insufficient drug on hand.

Prolonged penicillin blood levels to obviate need for daily dosage.

A single injection of benzathine penicillin G (1.2 million units) once a month provides continuous prophylaxis in most patients. Which is why it's recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever.

A method of choice in treatment of strep pharyngitis, too.*

In therapy of mild to moderate Group A streptococcal pharyngitis without bacteremia, just one injection of 600,000 to 900,000 units usually maintains penicillin serum concentrations in children for the 10 days necessary to eradicate the infecting organisms.† In adults, 1.2 million units are required.

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

have taken all of them.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM benzathine penicillin G.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Benzathine Penicillin G Therapy is indicated as Prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with benzathine penicillin G has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

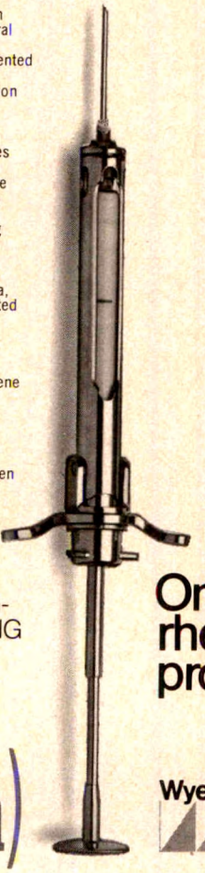
Composition: (units benzathine penicillin G as active ingredient): 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben and 0.14 mg. propylparaben.

600,000 units in 1-cc. TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

1,200,000 units in 2-cc. TUBEX, packages of 10, and in 2-cc. single-dose disposable syringe.

2,400,000 units in 4-cc. single-dose disposable syringe.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% povidone, 0.09% methylparaben and 0.01% propylparaben.



INJECTION

BICILLIN® LONG-ACTING

(sterile benzathine penicillin G suspension)

Once-a-month rheumatic fever prophylaxis.

Wyeth Laboratories
Philadelphia, Pa. 19101

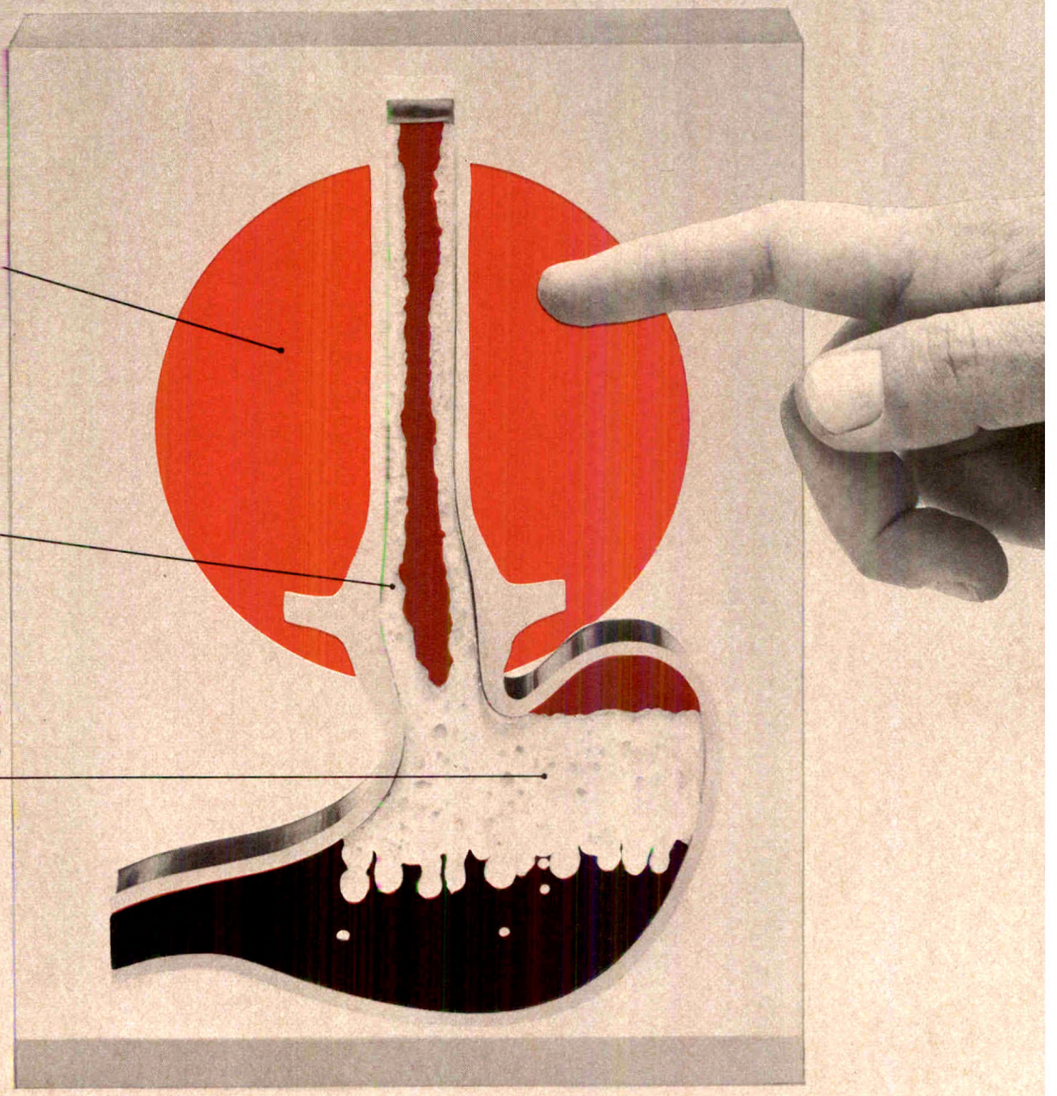
A-39

"This is the real Heartburn Zone. This is where GAVISCON® works!"

The Real Heartburn Zone
When gastric juice refluxes into the esophagus, stomach contents irritate sensitive nerve endings in esophageal mucosa to produce the pain of heartburn.

Gaviscon Coats
The Gaviscon foam coating clings to esophageal mucosa for pinpoint neutralization of gastric contents which might reflux from the stomach.

Gaviscon Floats
In the cardia and fundus of the stomach, GAVISCON® FOAMTAB® tablets form a soft, viscous layer of floating antacid foam that precedes gastric contents refluxing into the esophagus.



GAVISCON®

FOAMTAB®

(Alginic acid, 200 mg; aluminum hydroxide dried gel, 80 mg; magnesium trisilicate, 20 mg; sodium bicarbonate, 70 mg)
CHEWABLE ANTACID TABLETS for relief of heartburn accompanying hiatal hernia, gastroesophageal reflux, and esophagitis.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

SERIES 3500

EKG EXERCISE SYSTEM

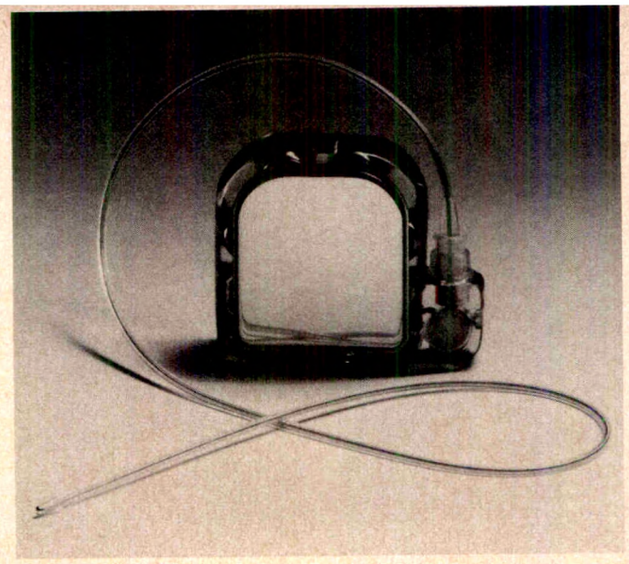
- New digital rate meter rejects noise, tremor, and tall T waves to provide precise 1% easily read rate display.
- Adjustable and automatic recording sequencer eliminates operator error and consequent need for stop watch.
- New Exercise Cable with buffer amplifiers provides noise free tracings.
- Complete 12-lead electrocardiogram in 10 seconds or classical/orthogonal in just 20 seconds before, during, and after exercise.
- Total patient safety under configurations currently specified by AAMI, N.F.P.A., U.L. and C.S.A.
- PRESSURE-SCRIBE ™ dry ink recording provides EKG's of superior readability with lowered cost per tracing.

marquette

...biomedical systems worldwide

3712 W. Elm St., Milwaukee, Wis. USA 53209

SURE-SCRIBE ™ is a trademark of Marquette Electronics, Inc.



Physicians Ask Us, "Who Is ESB Medcor?"

Two years ago, ESB Incorporated and Medcor, Inc. formed ESB Medcor, Inc. to bring to the medical profession a series of unique products for the field of cardiology.

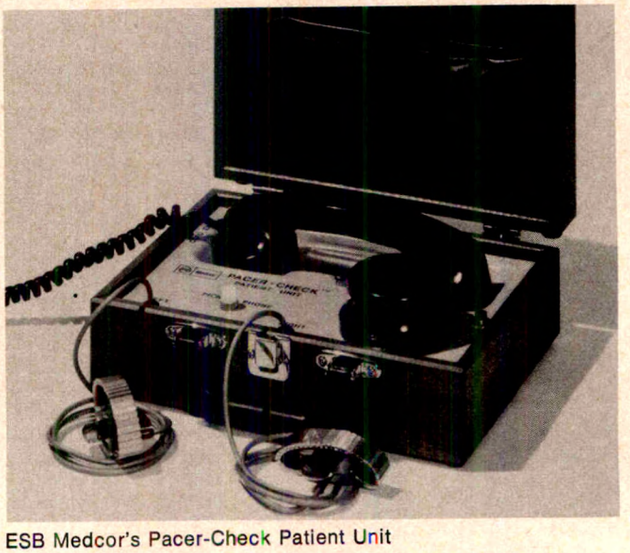
ESB Incorporated, the world's largest battery company with expertise in electrical, electro-chemical and chemical products, is best known for its Ray-O-Vac, Exide and Willard brand products. Over a period of years, it has carried out research and development in cardiac pacing as well as monitoring the critical parameters of patients with pacers. While this does represent a marked departure from ESB's major thrust, it is apparent that much of ESB's technical expertise has direct application in the medical field.

Medcor, Inc., a new name in medical electronics, has brought together some of the finest and most experienced technical talent in the field of cardiac pacing. This group has developed a line of pacer related products, including a unique heart pacer which utilizes a 'fail-safe' battery system and minimum current drain circuit to achieve greater reliability and longer life.

ESB Medcor, Inc. unites the strengths of both companies, and offers a systems approach to the treatment of pacer patients through its advanced cardiac pacers and the Pacer-Check System.

For further information about ESB Medcor, Inc. write: P.O. Box 6699, Hollywood, Florida 33021. Or call: (305) 791-8310.

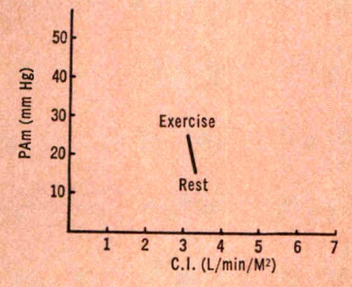
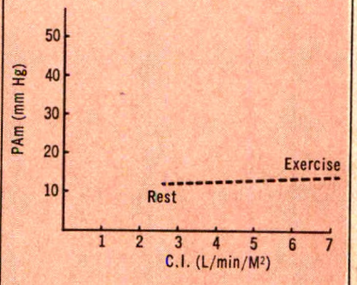
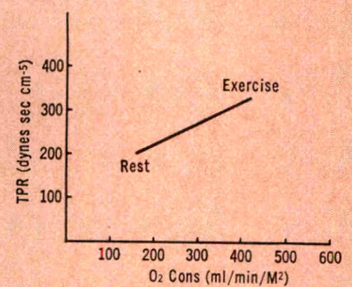
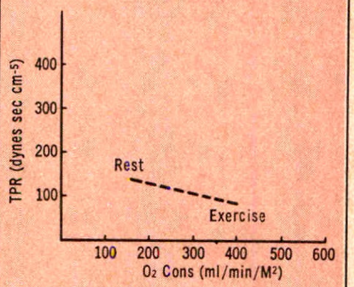
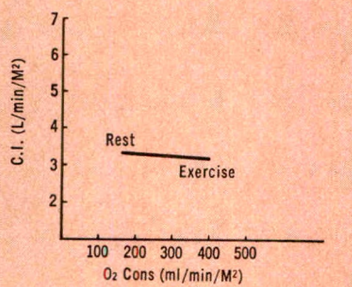
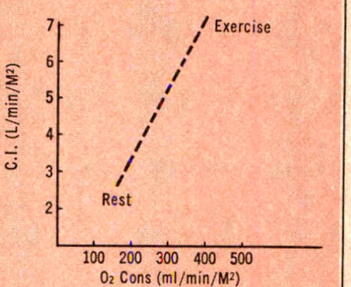
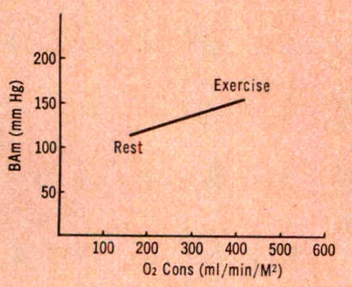
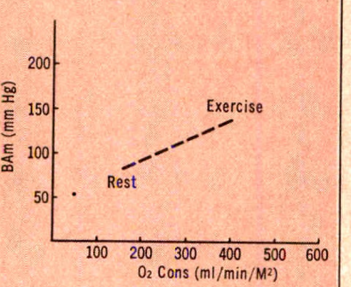
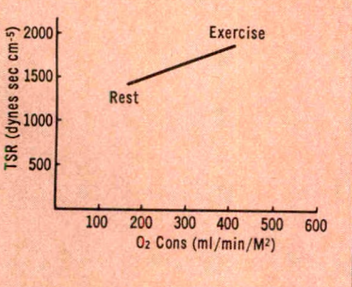
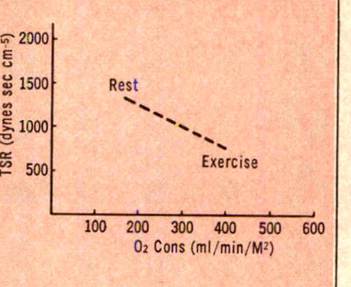
ESB Medcor's Pacer-Check Medic Unit



ESB Medcor's Pacer-Check Patient Unit

ESB Medcor™

HEMODYNAMICS OF ANGINA PECTORIS* — PATIENTS RESTING AND EXERCISING, BEFORE AND AFTER ISORDIL® SUBLINGUAL
(isosorbide dinitrate)

BEFORE MEDICATION		AFTER 5 mg. ISORDIL SUBLINGUAL (isosorbide dinitrate)
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

IN ANGINA PECTORIS*

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday stress

ISORDIL® SUBLINGUAL
(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

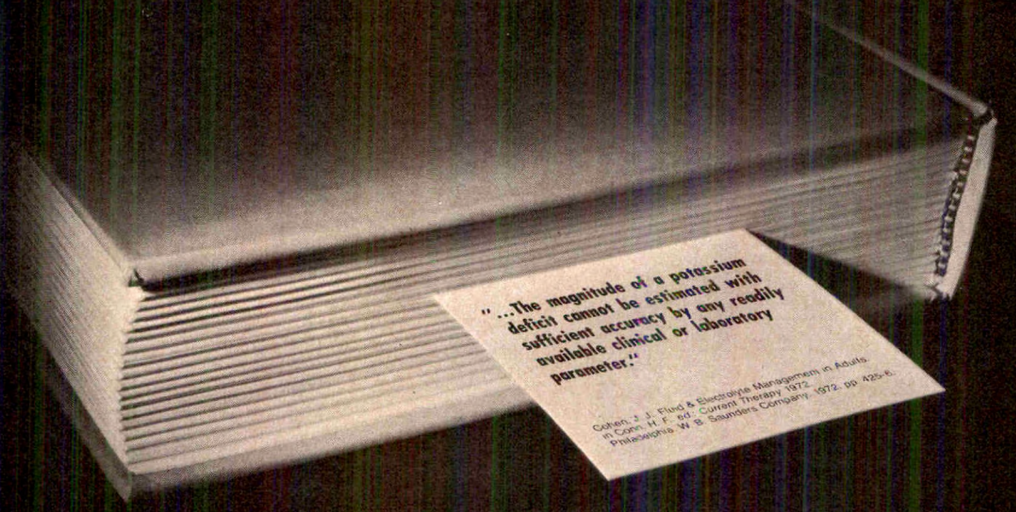
Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

IVES LABORATORIES INC.
New York, N.Y. 10017
DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.

HIDDEN HYPOKALEMIA



Prescribe good-tasting

K^+LORVESS®

effervescent tablets

Each tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g.

1:1 ratio K^+ and Cl^- in solution

SIMPLE TO TAKE—Tablets dissolve in 3-4 oz. cold water

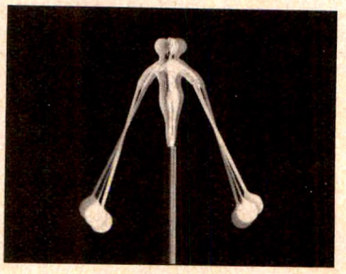
SPARKLING TASTE APPEAL—Fruitlike flavor

PATIENT ACCEPTANCE—Reduces chance of G.I. irritation. No added calories.

UNIT DOSE CONVENIENCE—Tablets individually foil-wrapped

KLORVESS offers what you and the patient like

Dorsey
LABORATORIES
Division of Sandoz-Wander, Inc.
Lincoln, Nebraska 68501



KLORVESS®
Effervescent Tablets

Description: Each dry effervescent tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g. Solution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate, and l-lysine hydrochloride.

Indications: For prevention or correction of potassium depletion and hypokalemic alkalosis. Especially useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each tablet completely in the stated amount of water.

Adverse Reactions: Vomiting, diarrhea, nausea and abdominal discomfort may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, and tall, peaked T waves.

Dosage and Administration: Adults: 1 tablet (20 mEq. each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water 2 to 4 times daily depending upon the requirements of the patient. The approximate minimum adult daily requirement of potassium is 40 mEq. Deviations from this recommendation may be indicated, since no average total daily dose can be defined but must be governed by close observation for clinical effects.
NOTE: Klorvess should be taken with meals.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

How Supplied: Klorvess Tablets (white, round) in boxes of 60 (2 Rx units of 30, NDC 43-100-87). Each tablet is individually foil wrapped.

THE AMERICAN JOURNAL of CARDIOLOGY

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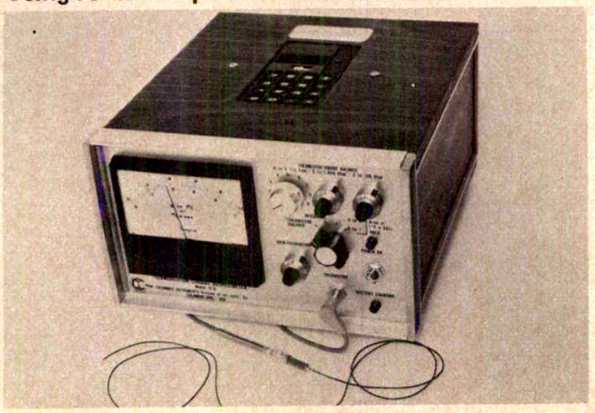
THERMODILUTION

Using room temperature indicator!



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- An intermediate instrument between the simple bridge and full scale computer.
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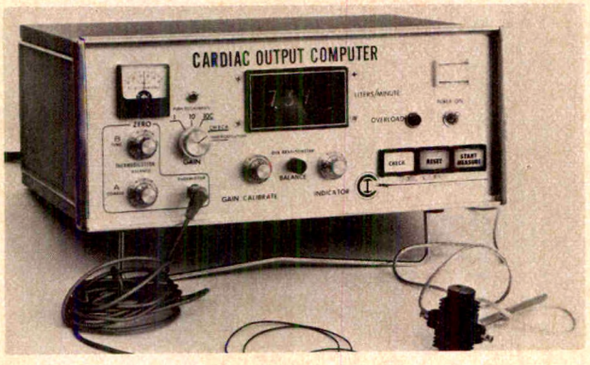

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Telephone: (614) 488-6176

Pronestyl® Capsules/Injection

(Procainamide Hydrochloride)

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 g. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

How Supplied: Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg. and 500 mg. are available in bottles of 100 and 1000 and Unimatic* Single Dose packaging in cartons of 100. Capsules providing 375 mg. are available in bottles of 100. Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) providing a 10% sterile aqueous solution (100 mg./cc.) with 0.9% (w/v) benzyl alcohol is available in 10 cc. vials.

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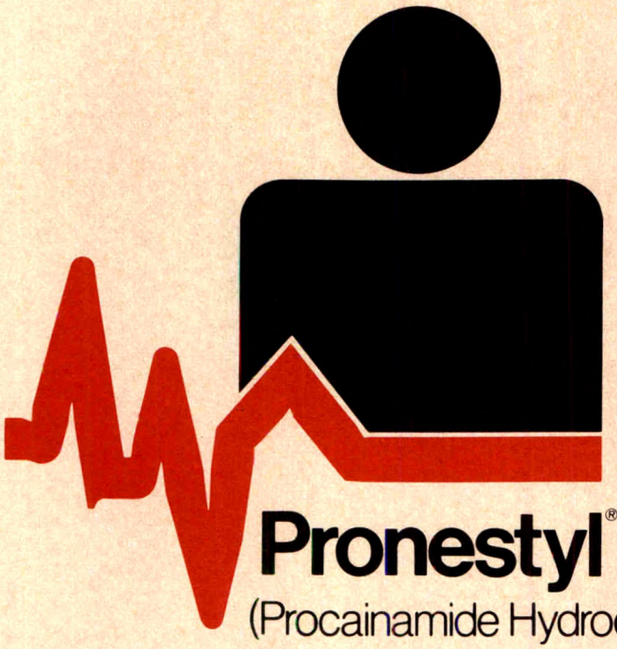
At the first sign of trouble



Pronestyl®

(Procainamide Hydrochloride)

for premature ventricular contractions

SQUIBB®

'The Priceless Ingredient of every product is the honor and integrity of its maker.'™

See opposite page for brief summary.

tolerance to exercise improved for angina patients

INDICATIONS: For the prophylaxis and long-term management of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

PRECAUTIONS: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

SIDE EFFECTS: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound.

Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

SUPPLIED: 10 mg. chewable tablets. Bottles of 100. Also 5, 10 and 15 mg. scored tablets in bottles of 100 10 mg. scored tablets also supplied in bottles of 1000.

Also available: Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital (Warning: may be habit-forming).

Cardilate®
(erythrityl tetranitrate)

chewable tablets 10 mg.
t.i.d. or q.i.d. (p.r.n.)
an effect appears in approximately 5 minutes —total duration of effect up to 4 hours.

Complete literature available on request from Professional Services Dept. PML.

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Research Triangle Park
North Carolina 27709

Is Sublingual Nitroglycerin still the drug of choice for acute angina?

Most physicians agree that of the nitrates available for the relief of acute angina pectoris, sublingual nitroglycerin remains the drug of choice. However, nitroglycerin is an unstable compound that can migrate from tablet to tablet, from tablet to cotton packing, from tablet to air.

And your patient may end up with too little nitroglycerin—just when it's needed most. To help solve this problem, Parke-Davis has developed Nitrostat, a stabilized sublingual nitroglycerin.

Nitrostat offers these important benefits:

- Rapid relief of pain
- Predictable patient response
- Uniform potency from tablet to tablet
- Stable sublingual dosage
- Reliable in clinical confirmation of angina pectoris

So whenever you're confronted by a patient with acute angina, *think* nitroglycerin. But *write* Nitrostat.

NITROSTAT®... the dependable nitroglycerin
(nitroglycerin tablets, USP)
Sublingual Tablets

PARKE-DAVIS

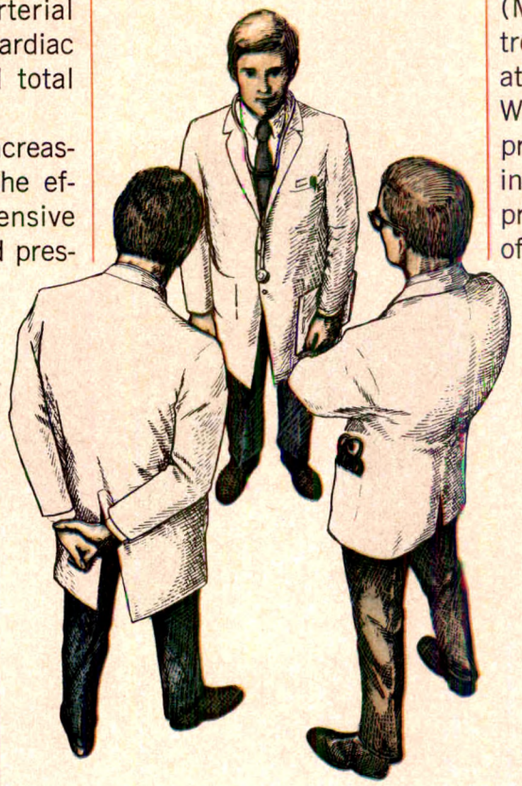
PD-JA-1045-1P (8-73)

Parke, Davis & Company
Detroit, Michigan 48232

The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

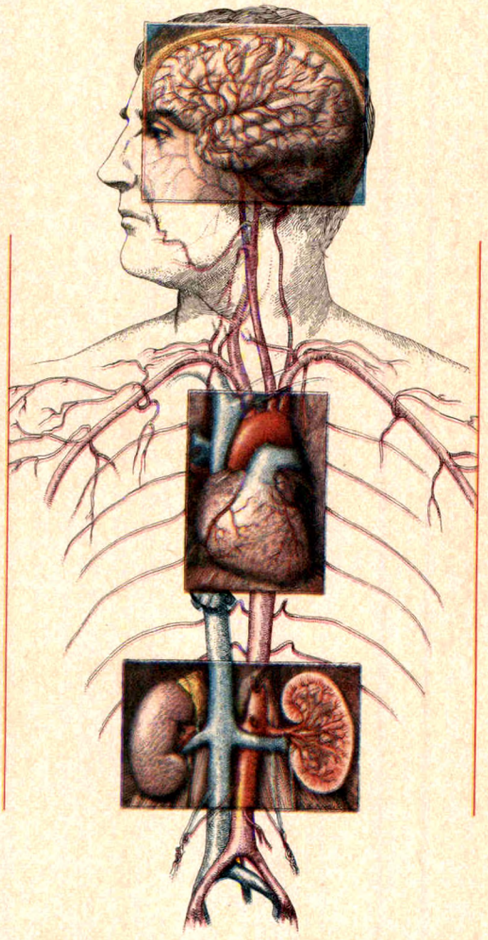
And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?



With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in

the more physicians rely on this unique antihypertensive



lowering blood pressure. But there are other considerations as well. Cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is actually slowed. Peripheral resistance is apparently reduced. ALDOMET does not usually compromise existing renal function; it generally does not reduce renal blood flow, glomerular filtration rate, or filtration fraction. And ALDOMET usually does not cause symptomatic postural or exercise hypotension.

Some patients on continuous methyldopa therapy may develop a positive direct Coombs test. For more details, see the brief summary of prescribing information.

Contraindicated in active hepatic disease and known sensitivity to the drug. Not recommended in pheochromocytoma or pregnancy. It should be used with caution in patients with a history of liver disease or dysfunction. Discontinue the drug if fever, abnormal liver function, jaundice, or acquired hemolytic anemia occurs.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

For a brief summary of prescribing information, please see following page.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: Acquired hemolytic anemia has occurred rarely in association with therapy with methyldopa. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of the anemia. Rarely, however, fatalities have occurred.

Some patients on continued therapy with methyldopa develop a positive direct Coombs test; incidence reported has averaged between 10% and 20%. It rarely occurs in first six months of therapy, and if not seen within twelve months, is unlikely to develop with continued administration. Positive Coombs test is dose-related; lowest incidence occurs in patients on 1 g methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa. Prior knowledge of a positive Coombs reaction aids in evaluation of cross match for transfusions. Patients with positive Coombs tests at time of cross match may exhibit incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with blood otherwise compatible in the major cross match may be carried out. If positive, advisability of transfusion with blood compatible in major cross match should be determined by hematologist or expert in transfusion problems.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy in several patients with liver dysfunction has shown microscopic focal necrosis compatible with drug hypersensitivity. Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen; reversible agranulocytosis has been reported. Methyldopa may interfere with measurement of creatinine by alkaline picrate method and of uric acid by phosphotungstate method. When used with other antihypertensive drugs, potentiation of antihypertensive action may occur.

Usage in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Perform periodic hepatic function tests and white cell and differential blood counts during first six to twelve weeks of therapy or in unexplained fever. Discontinue if fever, abnormalities in liver function tests, or jaundice appears. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Discontinue drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Anesthetics requirements may be reduced; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension may occur after dialysis because methyldopa is removed by this procedure.

Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Do not exceed recommended daily dose of 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure, including dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency, are seen occasionally. Angina pectoris may be aggravated. Symptoms of orthostatic and exercise hypotension may occur; if symptoms occur, reduce dosage. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distension, constipation, flatus, and diarrhea occur occasionally; these can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently; if edema progresses or signs of pulmonary congestion appear, discontinue drug. Rarely, urine exposed to air may darken due to breakdown of methyldopa or its metabolites. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression, reversible thrombocytopenia, drug-related fever and abnormal liver function studies with jaundice and hepatocellular damage (see **Warnings** and **Precautions**), rise in BUN, and a single case of bilateral Bell's palsy.

Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

MSD
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ADDENDUM

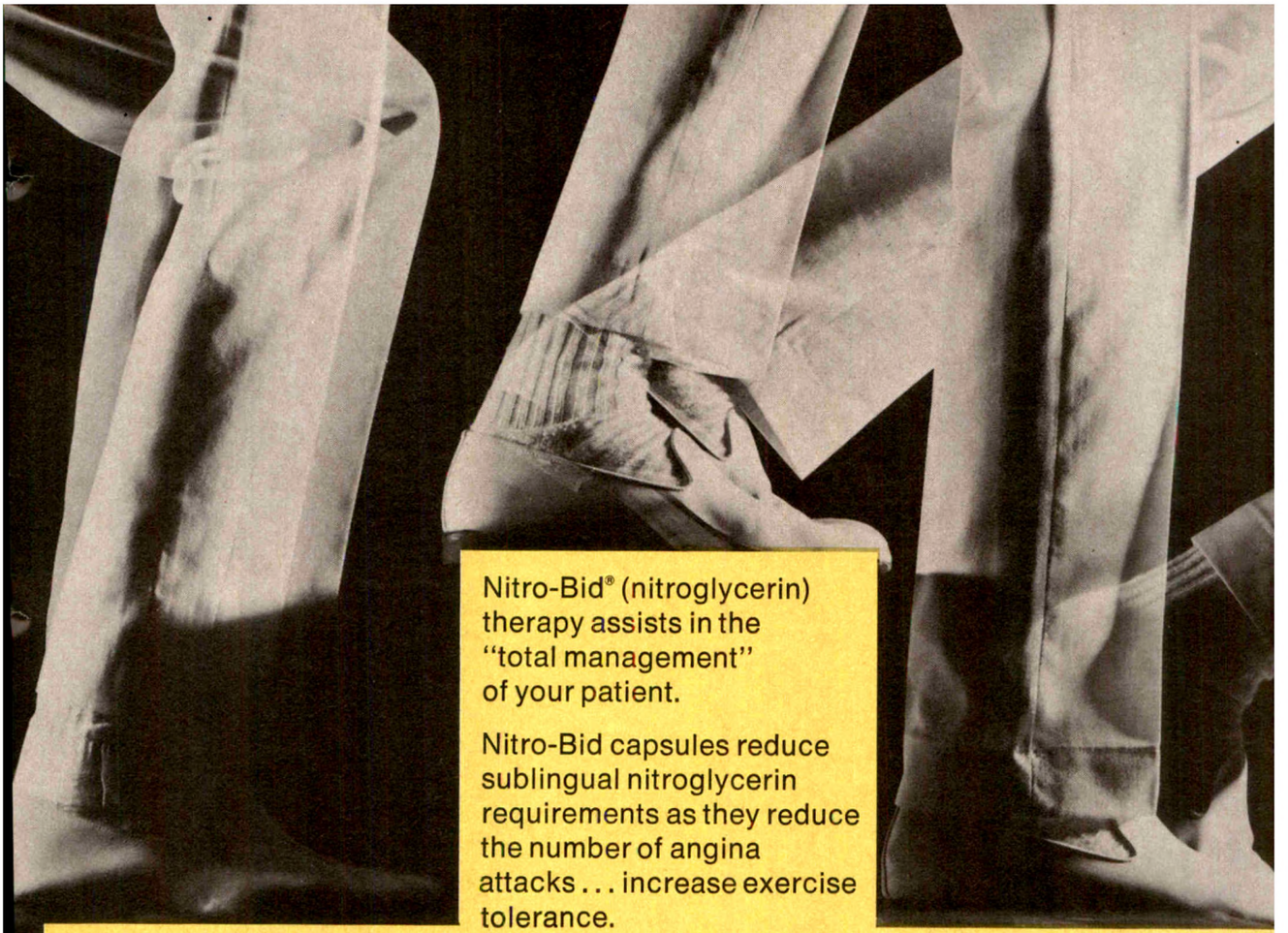
Let's make blood pressure "required reading" for all physicians.

With recent estimates that about 23 million Americans have high blood pressure—and that half of them are not even aware of it—detection of the problem in asymptomatic persons has become an issue of national importance.

Family physicians are being urged to take blood pressure readings as a matter of office routine, regardless of the presenting complaint or the reason for the visit. And because many people do not see a family physician for relatively long periods of time, some experts are suggesting that ophthalmologists, gynecologists, dermatologists, orthopedists, psychiatrists, dentists, school nurses, family planning counselors, and other health-care personnel make blood pressure reading a routine part of every examination or consultation.

Of course, a diagnosis of hypertension cannot be made on the basis of a single reading, but routine blood pressure readings can uncover potential trouble in a certain proportion of patients. And when trouble is suggested, further evaluation can be pursued more effectively.

Blood pressure—"required reading" for all physicians.



Nitro-Bid® (nitroglycerin) therapy assists in the "total management" of your patient.

Nitro-Bid capsules reduce sublingual nitroglycerin requirements as they reduce the number of angina attacks . . . increase exercise tolerance.

The Third Step in Angina.*

After the classic "2-Step" Test aids in a diagnosis of angina, sustained-release Nitro-Bid® (nitroglycerin) is a logical third step. Here's why.

In angina secondary to arteriosclerotic heart disease, sustained-release Nitro-Bid Plateau CAPS® provide a metered sequence of medication during the night to protect against nocturnal angina attack.

In titrating dosage, availability of different strengths "...is quite an asset..."[1]

Nitro-Bid 2.5 and Nitro-Bid 6.5 capsules afford two dosage strengths for convenience in increasing or decreasing dose to accommodate patient symptoms.

NITRO-BID® 2.5
(nitroglycerin 2.5 mg)
Plateau CAPS®

NITRO-BID® 6.5
(nitroglycerin 6.5 mg)
Plateau CAPS®

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

*"Possibly" effective:
For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12 hour intervals.
Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY MISSOURI 64137

For the prevention of the gripping pain of angina*
Peritrate® SA
Sustained Action (pentaerythritol tetranitrate) 80 mg
A logical choice for the "new" patient with angina pectoris.
*This drug has been evaluated as possibly effective for this indication.
See brief summary on following page.

Peritrate® SA

Sustained Action
(pentaerythritol tetranitrate) 80 mg

Description: Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate) is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates, may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur. In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature: (a) Cutaneous vasodilatation with flushing. (b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. (c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, bottles of 100 and 1000 tablets.

Additional Dosage Forms: Peritrate (pentaerythritol tetranitrate) 10 mg and 20 mg tablets in bottles of 100 and 1000.

Warner-Chilcott
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950

PE-GP-11-R1

February, 1974

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An implantable R-wave-inhibited pacemaker for intracardial and myocardial stimulation for a low, constant stimulation threshold.*

Low energy consuming circuitry and the new Mallory cell producing up to 4 to 5 years operating life.

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FEBRUARY 1974

The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 2

CLINICAL STUDIES

Natural History of Severe Proximal Coronary Artery Disease as Documented by Coronary Cineangiography

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Studying the natural history of patients with severe proximal coronary arterial lesions may assist evaluation of coronary revascularization surgery. We reviewed the mortality statistics of 469 patients with 80 to 100 percent occlusive lesions in the proximal coronary tree as diagnosed by selective angiography. Only patients with normal or moderately impaired left ventricular function were included in the study; patients with severe cardiomegaly, congestive heart failure or severe left ventricular impairment by left ventriculography were excluded. Follow-up periods ranged from 6 to 11 years for 178 patients with single vessel disease, 177 with double vessel disease and 114 with triple vessel disease. Patients with isolated disease of the left anterior descending artery had a 4 percent average yearly attrition rate or a 6 year mortality rate of 25.5 percent (17 of 69). Those with isolated disease of the right coronary artery demonstrated only a 2.3 percent yearly attrition rate or a 14 percent mortality rate in 6 years (11 of 77). Patients with double and triple vessel disease had, respectively, 41.5 and 63 percent 6 year mortality rates.

Survival was related to the number of vessels involved. Patients with single vessel disease of the left anterior descending artery had a significant annual mortality rate. The prognosis improved when good angiographic collateralization was present, particularly in single vessel disease with total occlusion. Functional disability, classified according to the New York Heart Association criteria, was related to mortality rates and proved a useful indicator in large patient groups. Prior myocardial infarction, location of the lesion above or below the major septal perforator in left anterior descending artery disease, and left main trunk lesions did not alter the prognosis significantly.

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The purpose of our investigation was to determine survival and mortality rates in patients with severe proximal coronary arterial lesions documented by angiography. These patients received medical treat-

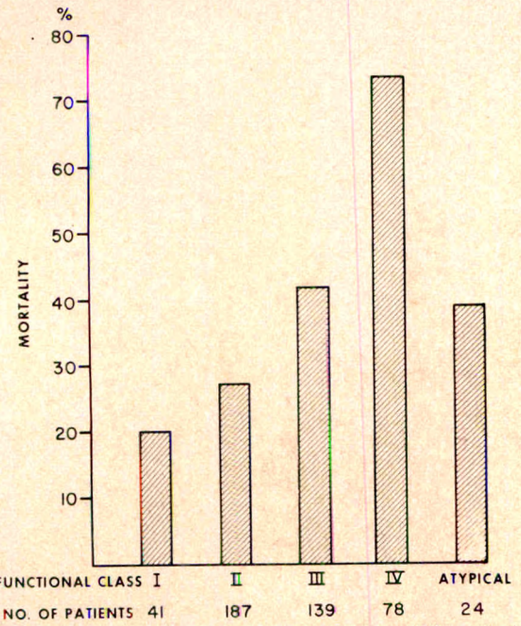

FIGURE 1. Functional class (New York Heart Association criteria) at time of cardiac catheterization related to 6 year mortality rates.

ment only. Patients with severe proximal lesions are often amenable to surgical intervention, and a study of their survival rates may help evaluate present and future surgical treatment for coronary artery disease.

Methods

Our angiographic criteria for case selection divided the series into three major groups: patients with single, double and triple vessel disease. Single vessel disease was defined as 80 to 100 percent occlusion of the right coronary, left anterior descending or left circumflex artery, and 50 percent or less reduction in lumen caliber in the other two vessels. Double vessel disease was considered 80 to 100 percent occlusion of two vessels with 50 percent or less obstruction in the third vessel. Triple vessel disease constituted 80 to 100 percent occlusive disease in all three major coronary arteries.

Ventriculography was not performed in 18 percent (88 of 469) of our patients in the early era of coronary arteriography but became a routine part of the examination by 1964. Patients with congestive heart failure, severe cardiomegaly or severe left ventricular impairment determined by left ventriculography were excluded, as were all patients with associated rheumatic or other cardiac disease. Only those with severe proximal lesions in dominant or major coronary arteries supplying the left ventricle were included in this study. Thus, a patient with a severe proximal lesion in a nondominant right coronary artery was excluded. Isolated left main trunk lesions were classified as double vessel disease of the left anterior descending and circumflex arteries. The Sones-Shirey cineangiographic technique was employed using selective injections in the right and left coronary arterial systems in multiple right and left anterior oblique views. Left ventricular angiography was usually performed in the right anterior oblique projection, and the left anterior oblique view was also obtained in patients with significant lesions of the left circumflex artery.

The completed follow-up study included 469 patients (424 men and 45 women) selected from 3,527 patients studied in the Cleveland Clinic Cardiac Laboratory between 1960 and 1965. During these years surgical treatment of coronary artery disease was in its infancy, and only a few patients underwent single internal mammary artery implantation for left anterior descending artery lesions. By present criteria, most of these 469 patients would be candidates for bypass graft surgery. Follow-up data were obtained by reviewing hospital and outpatient department records when available, and by letter or telephone communication with the referring physician and the patient or, when necessary, the patient's family. Of a total of 526 patients fulfilling the criteria, 469 (89.2 percent) were followed up for a minimum of 6 years (range 6 to 11 years).

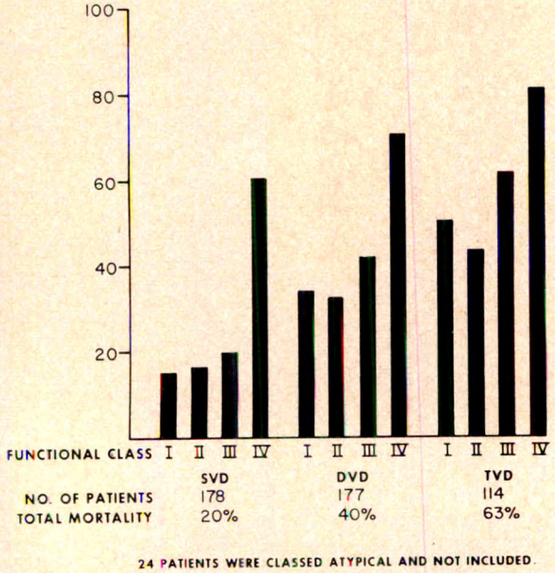

FIGURE 2. Six year observation of mortality related to functional class in patients with single (SVD), double (DVD) and triple (TVD) vessel disease. Percent mortality is on the ordinate.

Results

Our method of study resulted in different survival rates in each group. There was consistent agreement in assessment of the severity of the lesions by experienced interpreters using direct visual evaluation of the cineangiographic study. Opinion of even experienced observers is more variable when evaluating milder obstructive lesions. Finally, the simplicity of our criteria provided a basis for quick, easy communication and comprehension. Obviously, this is a clinical model used to evaluate survival statistics in a selected group of patients.

The 469 patients ranged in age from 28 to 69 years (median 49 years). The group can be characterized as white men aged 40 to 60 years with an average 2 year (range 2 months to 13 years) duration of symptoms before catheterization.

Relation between functional class, severity of disease and mortality: Patients were classified by functional capacity using the New York Heart Association criteria. The status of 24 patients was classified as atypical, characterized by bizarre chest pain or intermittent episodes of coronary insufficiency

with no symptoms between crises and no history of effort-related chest pain.

Figure 1 relates functional class to mortality. The majority of patients were in classes II and III. Mortality was related to the degree of functional disability; it was highest in patients with class IV angina. Figure 2 relates mortality to functional class and number of vessels involved. Patients with double and triple vessel disease, as anticipated, had the greatest functional disability and highest mortality rate. Relation of functional class to the presence of single, double and triple vessel disease (Fig. 3) demonstrated that 80 percent of class I patients had single vessel disease. Class II patients had predominantly single vessel disease and those in class III were equally divided among the three anatomic groups. Class IV patients usually had double or triple vessel disease. Thus, functional class is generally useful in predicting degrees of anatomic disease in large patient groups but, unfortunately, not in an individual patient. During the 6 year period of observation, the 288 survivors generally experienced an episodic course with exacerbations and remissions, and it was rare for a patient to remain asymptomatic. Thus, our subjects represent a broad spectrum of patients with symptomatic angina and all degrees of disability. Figure 4 summarizes the patients' functional status at the onset of the study and 6 years later according to the number of vessels involved.

Survival rates related to extent of coronary disease: One cannot assume all deaths were cardiac in origin but, in almost all cases, information received from the referring physician or the patient's family suggested that death was due to coronary artery disease. A survival curve for 1960 to 1965 for the American white male population aged 49 years and older reveals a 1 percent yearly attrition rate or a 6 1/2 percent total mortality rate in 6 years (U. S. Office of Vital Statistics). Thus, we can anticipate 30 deaths in 469 persons in the general white male population. By comparison, there were 181 deaths and a 6 year mortality rate of 38.3 percent in our series, a figure six times the anticipated death rate.

Figure 5 shows the life survival curves in patients with single, double and triple vessel disease; the calculated mortality rates were 20, 40 and 63 percent, respectively, for the three anatomic groups during the 6 year study period. Death occurred in 36 of 178 patients with single vessel disease, 73 of 177 with double vessel disease and 72 of 114 with triple vessel disease. Calculation of the average yearly attrition rate results in respective annual mortality rates of 3.3, 6.6 and 10 percent for the three groups.

Figure 6 shows the life survival curves for the 6 year study period in the subgroups with single vessel disease. There were 11 deaths in the 77 patients with right coronary artery disease (2.3 percent average yearly attrition rate). Patients with disease of the left anterior descending and left circumflex arteries experienced a considerably higher average annual mortality rate (4 percent for patients with left anterior descending artery disease and 4.2 percent for those with

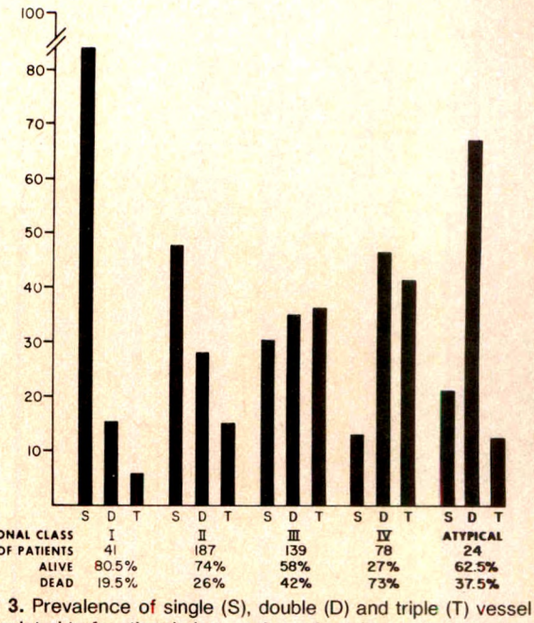

FIGURE 3. Prevalence of single (S), double (D) and triple (T) vessel disease related to functional class at time of cardiac catheterization, and 6 year mortality rate. Prevalence rate is on the ordinate.

left circumflex artery disease). Although the latter group was small, 8 of the 32 patients died, all over the age of 50 years. Patients with single vessel disease of the left anterior descending artery had a significant mortality rate at all ages.

There were three possible combinations or subgroups of patients with double vessel disease. Disease of the left anterior descending and right coronary arteries was the most common combination in our series, a finding consistent with the well known frequency of disease in the proximal left anterior descending and right coronary arterial systems. Mortal-

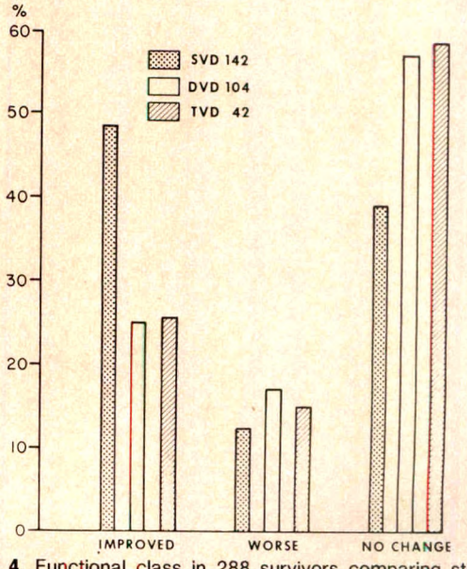

FIGURE 4. Functional class in 288 survivors comparing status at onset of study and 6 years later. SVD, DVD and TVD = single, double and triple vessel disease, respectively.

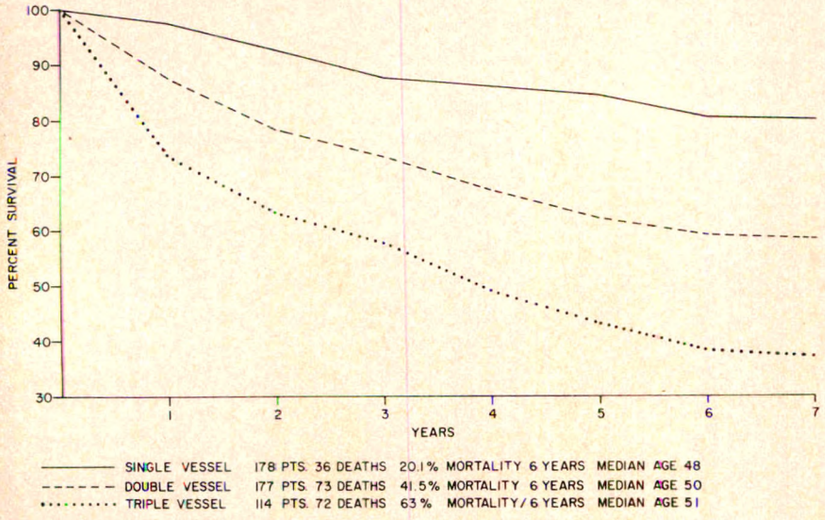

FIGURE 5. Survival rates in patients with single, double and triple vessel disease, at time of angiographic diagnosis. The lumen caliber was compromised 80 percent or more in each involved vessel.

ity rates were 35.4 percent (17 of 48) in patients with combined right coronary and left circumflex artery disease, 47 percent (24 of 51) for those with left anterior descending and left circumflex artery disease, and 41 percent (32 of 78) for those with right coronary and left anterior descending artery disease. Patients with combined lesions involving the left anterior descending artery had a slightly higher mortality rate than those with combined right coronary and left circumflex artery disease. However, mortality differences were not statistically significant among patients with the three combinations of double vessel disease.

Twenty-nine patients in our series had severe left main trunk lesions, 8 patients with isolated lesions and 21 with associated severe right coronary artery disease. The mortality rate was 50 percent (4 of 8) in patients with isolated left main trunk lesions and 71 percent (15 of 21) in those with associated right coronary artery disease. During the 6 year study period, the mortality rate was 47 percent for patients with combined left anterior descending and left circumflex artery disease and 63 percent for those with triple vessel disease. Thus the mortality rate was only slightly higher when a significant left main trunk lesion was present.

Those patients with left main trunk lesions underwent selective cardiac catheterization. Two patients in the group with combined left main trunk and right coronary artery disease died 1 and 3 days, respectively, after catheterization. These two deaths might have been related to catheterization, although both patients had coronary insufficiency and had class IV status before catheterization. Clinically, they seemed to tolerate the procedure well. In a previously reported series,[1] the mortality rate at the time of cardiac catheterization was 15.6 percent (5 of 32) in patients with severe left main trunk disease.

Left main trunk lesions must be treated with respect, and proper angiographic technique should

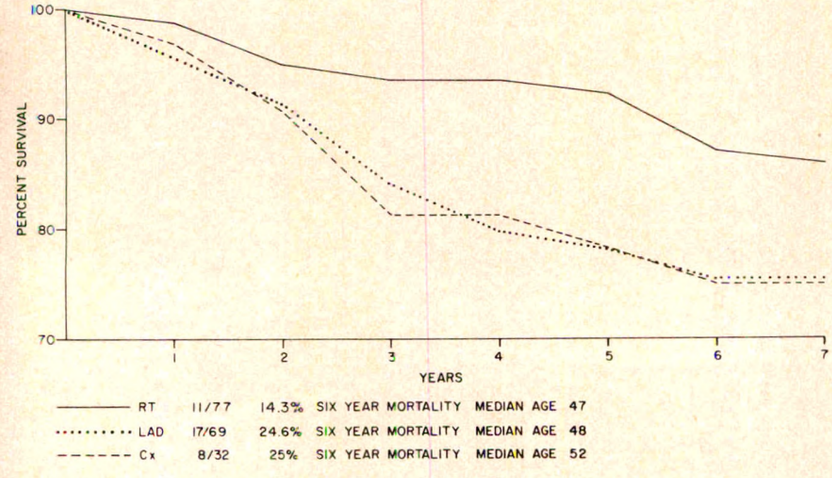

FIGURE 6. Survival rate in subgroups with isolated disease of the right coronary (RT), left anterior descending (LAD) or left circumflex (Cx) artery. Lumen obstruction was 80 percent or greater, as calculated at the time of angiographic diagnosis.

limit the number of injections in the ostium to those required for accurate diagnosis. However, caution and extreme care is necessary for all patients with triple vessel lesions or class IV status, or both. Our experience indicates that selective injection by the Sones-Shirey technique is safe in patients with left main trunk lesions when performed with due caution.

Age and sex: Factors that may influence survival are age, sex, presence of collateral circulation, location of the lesion above or below the major septal perforator in patients with left anterior descending artery disease, and prior myocardial infarction.

The death rates, in all decades, of patients with double and triple vessel disease were similar. This was also true of patients with single vessel disease of the left anterior descending artery. Figure 7 depicts mortality plotted against age before and after age 50. All patients with left circumflex artery disease died after age 50, and only 4 patients with right coronary artery disease died before age 50. The mortality in the group with left anterior descending artery disease was 23 percent before age 50 and 27 percent after age 50. Thus, age does not appear to influence survival in left anterior descending artery disease, perhaps indicating a more rapid rate of progression of disease in these patients.

As a group, women were equally affected by single, double and triple disease, and the death rate was parallel to that of men.

Collateral circulation: Collateral blood supply demonstrated by angiography was correlated with survival. We divided collateral circulation into two major categories. Good collateral supply was defined as clear opacification of the main trunk of an occluded or severely narrowed major coronary artery beyond the lesion and usually from a contralateral source. Poor collateral supply was defined as minimal or no opacification of the obstructed artery, with or without slight opacification of small secondary branches.

Figure 8 relates mortality to age and the presence or absence of good collateral blood supply demonstrated angiographically. Mortality from triple vessel disease was 63 percent in all age groups with or without angiographic evidence of good collateral circulation. In the group with double vessel disease, mortality rate was 38 percent in patients with good collateral circulation and 54 percent in those with poor collateral circulation (P <0.04). The mortality rate of patients with single vessel disease and good collateral supply was 15 percent in all age groups. That of patients with single vessel disease and poor or no collateral supply was also 15 percent before age 50; after age 50 the rate increased to 50 percent (P <0.00002). Thus, the older patients with single vessel disease and poor collateral supply did not fare well.

An important factor in evaluating collateral circulation is determining whether its source of origin is compromised or uncompromised. Usually the collateral blood supply arises from a contralateral coronary arterial source. Thus, in our series of patients with

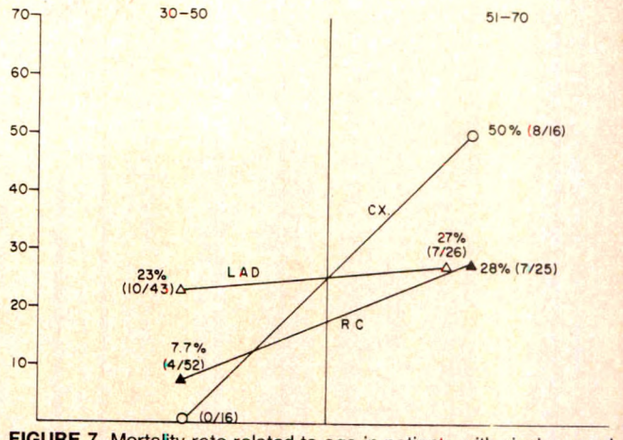

FIGURE 7. Mortality rate related to age in patients with single vessel disease. CX. = left circumflex artery; LAD = left anterior descending artery; RC = right coronary artery.

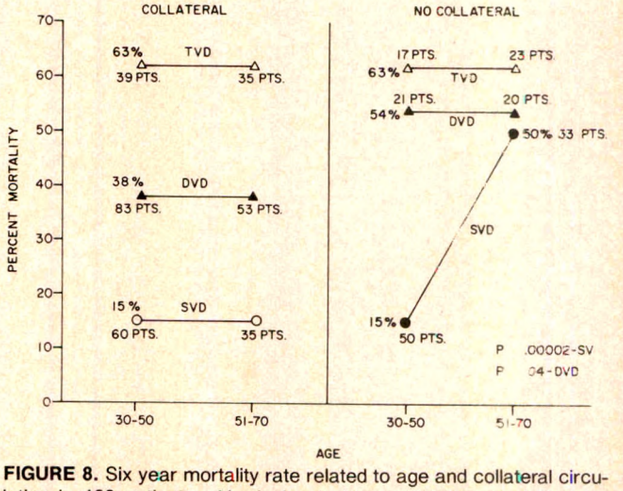

FIGURE 8. Six year mortality rate related to age and collateral circulation in 469 patients with single, double and triple vessel disease. SVD, DVD and TVD = single, double and triple vessel disease, respectively.

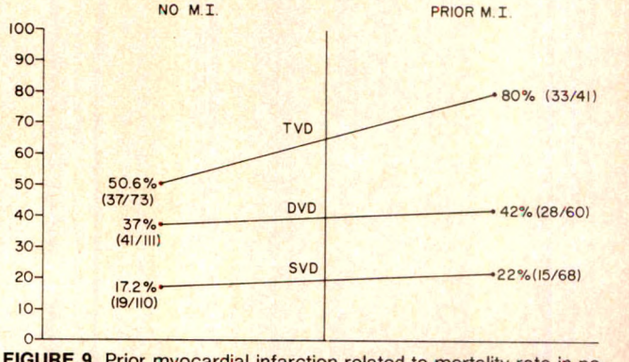

FIGURE 9. Prior myocardial infarction related to mortality rate in patients with single, double and triple vessel disease. SVD, DVD and TVD = single, double and triple vessel disease, respectively; M. I. = myocardial infarction.

single vessel disease collateral circulation was uncompromised at the time of the study. Patients with double and particularly those with triple vessel disease often have collateral circulation, but this is frequently compromised. Seventy percent of patients with double and triple vessel disease had angiographic evidence of collateral supply, indicating an intrinsic compensatory attempt to maintain adequate coronary perfusion. Previous reports[2–6] have demonstrated increased collateral blood supply in patients with double and triple vessel disease. Another interesting facet of single vessel disease and collateral protection was demonstrated in the 82 patients in our series with total occlusion of a single coronary artery. Eighteen patients in this group had poor collateral circulation manifested by angiography and 10 died during the 6 year study period, compared to 5 of the 64 patients with good collateral circulation, again demonstrating the protection offered by good uncompromised collateral blood supply.

Proximal vs. peripheral lesions: Empirically, severe lesions located proximal to the major septal perforator of the left anterior descending artery have been considered more serious than lesions peripheral to the major septal perforator. In our series of 69 patients with left anterior descending artery disease, 24 had the lesion above the major septal perforator, or compromising the ostium of the perforator, and 45 had the lesion below the major septal perforator. Mortality was 29 percent (7 of 24) in the first group and 21 percent (11 of 45) in the second group. Thus, the mortality rate was only 7 percent higher in patients whose lesion was in the more proximal position. The difference is not statistically significant.

Prior myocardial infarction: The number of vessels involved appears to be a more significant prognostic indicator than prior myocardial infarction. Prior myocardial infarction was defined as electrocardiographic evidence of transmural infarction, which was almost always supported by angiographic findings of scar tissue replacement. Patients with previous infarction and single and double vessel disease had the same survival rate as those without prior myocardial infarction. However, in those with triple vessel disease, mortality appeared greater in cases of prior myocardial infarction (Fig. 9). Since patients with triple vessel disease have a decompensated and threatened coronary circulation, it is not surprising that prior myocardial infarction might be an unfavorable prognostic sign.

Discussion

Clinical application of these data may be premature. However, surgical intervention in patients with double and triple vessel disease appears indicated because of the high average yearly attrition rate and poor 6 year prognosis with medical therapy only. Patients with double and triple vessel disease had 40 and 63 percent mortality rate, respectively, in 6 years. Relief of anginal disability is also a major goal in these patients.

Single vessel disease is a more complex problem. Prognosis appears to be excellent in patients with total occlusion of one vessel and good, uncompromised collateral blood supply and in patients with isolated lesions of the right coronary artery. Asymptomatic patients in these two groups are probably best managed medically. Since isolated disease of the left anterior descending artery is more lethal (4.0 percent average yearly attrition rate), surgical relief of the obstruction is more urgent unless uncompromised collateral circulation is present.

A study by Friesinger et al.[7] demonstrated an excellent prognosis in 32 patients with single vessel disease. However, the mean age of their patients was only 39.2 years and the severity of the lesion was poorly defined, ranging from 50 to 100 percent reduction in lumen caliber. In addition, no attempt was made to evaluate collateral blood supply and its possible role in increasing longevity. The total group was small, with even smaller subgroups, and the duration of the follow-up period averaged 54 months only. Therefore generalizations regarding prognosis from these data may be hazardous and may provide a false sense of security.

The ultimate role of surgery and other forms of treatment for coronary artery disease will be determined by careful follow-up of patients who have a clear morphologic diagnosis established by selective coronary angiography.

Addendum

Utilizing the data reported here as a control or comparison group Sheldon et al.[8] found improved longevity and functional status in a large group of patients who received bypass vein graft procedures for severe coronary arterial lesions. We hope that this basic information will prove of some value in evaluating current surgical interventions and perhaps newer evolving surgical and medical therapy for coronary artery disease.

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Unstable Angina—Prospective and Randomized Study of Its Evolution, With and Without Surgery

Preliminary Report

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A prospective and randomized study of 142 patients was undertaken to evaluate medical or surgical treatment in patients with unstable angina. The condition of each patient was classified according to one of three categories: intermediate syndrome (44 patients); progressive angina with and wihout previous infarction (53 patients); and postinfarction angina (14 patients). Of the 142 patients, 31 were excluded on the basis of specific criteria. A detailed research protocol, which included early blind random choice of medical or surgical therapy, was followed.

The results indicate the following: (1) It is possible to conduct a randomized study of patients with unstable angina, grouped in comparable categories; (2) these groups were statistically homogeneous in relation to the variables examined; (3) in spite of a mean follow-up time of only 8.3 months, the natural history of patients with an intermediate syndrome differed from that of patients with progressive angina, thus justifying the distinction; (4) patients with an intermediate syndrome treated surgically appeared to have a significantly reduced mortality rate and those who have survived surgery are in better clinical condition than medically treated patients; and (5) no such differences were found in patients with progressive angina, but a longer follow-up period is warranted.

In the past few years cardiologists have had to evaluate promptly new methods of therapy for coronary disease. Fowler[1] outlined clearly the problem when he stated: "If someone does not now perform adequately controlled clinical trials of [a new] procedure, in 10 years many lives perhaps will have been needlessly sacrificed and information may still be lacking for an objective decision about the place of this procedure in the management of either acute or chronic coronary artery disease."

Massive experience with several thousands of patients[2] followed up over the years will soon allow a precise and definitive evaluation of the merits of surgical revascularization of the myocardium in patients with chronic coronary artery disease. Quite a different challenge is that of assessing the efficacy of such surgical treatment in patients with any of the main clinical patterns of acute coronary disease: unstable angina or acute myocardial infarction or its complications.

In considering unstable angina, the first major problem is the lack of objective criteria for precise diagnosis. This is best shown by the fact that between the extremes of chronic stable angina and acute myocardial infarction there are many patients with clinical, hemodynamic and electrocardiographic changes that follow one of several comparable patterns. Second, information pertaining to the natural history of unstable angina, particularly over an extended period of time, is scarce and unreliable. Finally, since it is not easy to collect a large number of patients with this clinical syndrome, each research

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TABLE I

Angiographic Index (in points)

Variable	Points
A. Occlusion by coronary arteriography	
Right coronary artery	
Proximal	+3
Medial	+3
Distal	+2
Left anterior descending artery	
Proximal	+7
Medial	+5
Distal	+1
Circumflex artery	
Trunk	+3
Lateral ventricular	+1
Atrioventricular	+1
Left main trunk	+10
B. Collateral circulation	
Good	−4
Poor	0
Absent	+4
C. Left ventriculographic data	
Grade I (normal)	0
Grade II (localized hypokinesia)	+4
Grade III (regional akinesia or dyskinesia)	+8
Grade IV (generalized hypokinesia)	+16

project is limited to the size of a significant sample selected with accurate clinical criteria.

With these considerations in mind, in July 1970 we started a prospective study of all patients with unstable angina admitted to our coronary care unit, using the most precise definitions available. We report here our research procedure, and the means by which patients were assigned to comparable groups for valuation of different therapeutic programs. Although the follow-up period is too short for definitive assessment, our initial results show significant trends.

Material and Methods

Classification of Cases

The study began in July 1970, and the statistical evaluation continued until December 1972. There were 142 patients, with an average follow-up period of 8.3 months. Patients older than 68 years were not included in the study.

Unstable angina was considered to comprise three major categories: an intermediate syndrome, progressive angina and postinfarction angina.

Intermediate syndrome: A patient was admitted to the study under this classification if all of the following major criteria and at least two of the minor clinical criteria were met.

Major criteria: (1) Recurrent angina pectoris, prolonged and intense, not related to effort; (2) absence of extracardiac accessory factors; (3) normal serum enzyme levels or elevation below 50 percent of the normal maximum or 50 percent above basal levels; and (4) absence of severe pump failure or severe prolonged arrhythmias.

Minor criteria: (1) Little or no response to administration of nitrites; (2) transitory electrocardiographic changes of ventricular repolarization; (3) transitory cardiac arrhythmias; and (4) an interval of less than 1 month between onset of angina and admission to this study.

Progressive angina: A patient was admitted to the study under this category if no more than 3 months before the study he had experienced a change in the evolutionary pattern of angina, with an increase in the intensity, duration and frequency of pain but without the requirements postulated for the intermediate syndrome.

Postinfarction angina: This group included all patients who began to experience anginal attacks within the first month after an infarction.

The groups with the intermediate syndrome and progressive angina were further subdivided into two subgroups, patients with or without a previous infarct. In all instances the acute infarct had to have occurred at least 3 months before admission to the study.

Excluded patients: This group included all patients who met the clinical criteria but were later disqualified on other grounds. In some, arteriography disclosed no obstructive coronary artery disease or only minimal lesions; others were not candidates for direct myocardial revascularization (see Table VII).

Plan of Study

Phase A: This phase comprised three stages:

Stage 1: A patient with symptoms of possible coronary disease was admitted to the coronary care unit for a complete clinical examination, electrocardiogram, chest roentgenogram, phonocardiogram (in some cases), multistage exercise test (when indicated) and laboratory tests (serial determinations of serum glutamic oxaloacetic transaminase [SGOT], creatine phosphokinase [CPK] and lactic dehydrogenase [LDH]). Once all the results were evaluated, and if the criteria for admision to the study were met, a medical or surgical program of therapy was determined by blind random choice. In some instances the patient was referred to us with a previous clinical or surgical indication which was followed, but in all patients the decision was made before the angiographic study.

Stage 2: An angiographic study was performed by the Sones technique with 35 mm coronary cineangiography (Sones) and left ventriculography. The condition of each patient was graded according to a scale (Table I) we designed to facilitate statistical analysis. Obstructive lesions of the coronary arteries were considered in relation to their site, with classification of the right and left anterior descending coronary arteries into three segments, and the circumflex artery into the trunk, atrioventricular and lateral ventricular branches. Only obstructive luminal lesions of 70 percent or more were graded, and only the most important lesion of each vessel was considered. Collateral circulation influenced the grading by the addition of 4 points if absent, no points if poor, and the substraction of 4 points if good. The left ventriculogram was also graded according to the degree of anatomic or functional contractile change demonstrated.

Stage 3: Each patient was then presented to the surgical staff for determination of his suitability as a candidate for a direct revascularization procedure. At this stage a patient not considered a suitable candidate was classified in the "excluded" group. The surgical staff ignored the randomly chosen therapeutic prescription as it considered each case.

After a patient was accepted by the surgeons he entered either the surgical or the medical treatment program according to the decision made in Stage 1. He was offered the best medical treatment available, or whatever procedure the surgeons decided upon.

Medical treatment was adapted to the clinical state of each patient, following our usual protocol which included (1) surveillance in the coronary care unit for a minimum of 5 days, or 96 hours after the last significant complication; and (2) administration of the following agents: (a) nitroglycerin and long-acting nitrites; (b) analgesic agents, including opiates, if indicated; (c) sedatives (Diazepam®); (d) oxygen; (e) anticoagulant agents (heparin) unless contraindicated, particularly in young patients, the obese and patients with venous disease or a history of myocardial infarction; (f) digitalis and diuretic agents, only if there were signs of cardiac failure; and (g) beta adrenergic blocking agents (propranolol, 40 to 100 mg daily, and, more recently, practolol, 200 to 400 mg daily) in the absence of cardiac failure and depending on the tolerance of the patient.

Phase B: After each patient was finally assigned to a treatment group, he was followed up carefully until his return home. He was then reevaluated every 4 months (clinical examination, electrocardiogram at rest and with effort, using an ergometric bicycle) and graded clinically according to our follow-up index (Table II). After a year of follow-up studies, a new hemodynamic study was performed whenever possible.

In summary, the plan of study was as follows:

Phase A
- Stage 1
  - A. Clinical diagnosis
  - B. Random choice of therapeutic program
- Stage 2
  - A. Hemodynamic study
  - B. Acceptance of the case by the surgical group
- Stage 3
  - Medical or surgical treatment, as determined in Stage 1B

Phase B
1. Follow-up at 4 month intervals
   - A. Clinical evaluation
   - B. Electrocardiogram at rest and with graded effort
   - C. Updating of follow-up index
2. Hemodynamic study when feasible after 1 year

Finally, the data were examined statistically to determine if, on the basis of age, electrocardiographic changes and hemodynamic findings (coronary cineangiography and left ventriculography) the patients who underwent surgical treatment were indeed comparable to those who received only medical care.

Results

Clinical Features

This analysis will be limited to the 97 patients with the intermediate syndrome or progressive angina since only 14 patients had postinfarction angina. The mean age of the 97 patients was 53.3 years (range 34 to 68 years). Only 3 patients were women (Table III). The calculated t and P values suggested that the sample was homogeneous and without significant differences among the groups.

Four main risk factors were considered: arterial hypertension, diabetes, cigarette smoking and hypercholesterolemia. Their prevalence was similar to that found in patients with other types of coronary disease, and there was no significant difference among the groups.

Previous angina pectoris was a feature in all patients with progressive angina, but was present in

TABLE II

Follow-Up Index (in points)

Variable	Points
A. Infarction	
ST-T	+3
QR	+7
QS	+10
B. Conduction defects	
LAH, 1° AVB	+1
AVB, 2° RBBB	+2
LPH	+3
3° AVB	+6
C. Arrhythmias (all types except conduction defects)	+2
D. Heart failure	
Grade I	+1
Grade II	+3
Grade III	+5
Grade IV	+9
E. Angina	
1+	+2
2+	+4
3+	+6
4+	+8
F. Increasing diabetes	+2
G. Blood pressure >200/120	+2
H. Weight increase >30%	+2
I. Serum cholesterol >350 mg	+2
J. Physical incapacity	
Slight	+1
Moderate	+3
Severe	+5

AVB = atrioventricular block; LAH = left anterior hemiblock; LPH = left posterior hemiblock; RBBB = right bundle branch block.

TABLE III

Distribution of Patients

	Patients				
	no.	Mean Age (yr)	t	P	Male Patients (no.)
A. Intermediate syndrome					
No previous infarction					
Surgical treatment	15	53.6	0.02	>0.90	15
Medical treatment	8	53.5			7*
Previous infarction					
Surgical treatment	9	53.2	0.40	≥0.70	9
Medical treatment	12	54.5			12
B. Progressive angina					
No previous infarction					
Surgical treatment	19	50.8	0.85	=0.40	18*
Medical treatment	10	54.1			10
Previous infarction					
Surgical treatment	14	52.2	0.75	≥0.46	14
Medical treatment	10	55.0			9*

* 1 female patient in each subgroup.
P = probability; t = Student's t test.

TABLE IV

Coronary Lesions

	1 Artery	2 Arteries	3 Arteries	χ^2	P*
A. Intermediate syndrome					
No previous infarction					
Surgical	5	6	4	0.035	>0.98
Medical	3	3	2		
Previous infarction					
Surgical	0	1	8	3.60	≥0.173
Medical	1	5	6		
B. Progressive angina					
No previous infarction					
Surgical	6	9	4	2.04	≥0.37
Medical	1	5	4		
Previous infarction					
Surgical	0	6	8	0.68	≥0.42
Medical	0	6	4		

* The value of "*P*" should be considered only approximate because of the small numbers of patients in the various subgroups.

TABLE V

Left Ventriculogram

	Type A	Type B	χ^2	P
A. Intermediate syndrome				
No previous infarction				
Surgical treatment	13	2	0.89	≥0.35
Medical treatment	5	3		
Previous infarction				
Surgical treatment	3	6	0.00	1
Medical treatment	4	8		
B. Progressive angina				
No previous infarction				
Surgical treatment	16	3	0.31	>0.60
Medical treatment	7	3		
Previous infarction				
Surgical treatment	5	9	1.20	>0.28
Medical treatment	1	9		

Type A = normal or minor abnormalities of wall motion; Type B = akynesia, dyskinesia or hypokinesia of 2 walls.

only 60 percent of those with the intermediate syndrome, being equal in each subgroup.

Electrocardiographic Findings

Basal electrocardiogram: There were no significant differences between patients with the intermediate syndrome and those with progressive angina, except for changes related to the presence or absence of a previous infarct. In all patients with the intermediate syndrome and no previous infarct there were changes of ventricular repolarization, most of them of the anterior wall. Eight patients with progressive angina and no previous infarction had a normal electrocardiogram.

Electrocardiogram during angina: The changes during an episode of angina pectoris in order of frequency were: (1) depression of S–T segment; (2) elevation of S–T segment (a finding more frequent in our series than in previously reported studies); (3) alterations of the S–T segment with arrhythmias; (4)

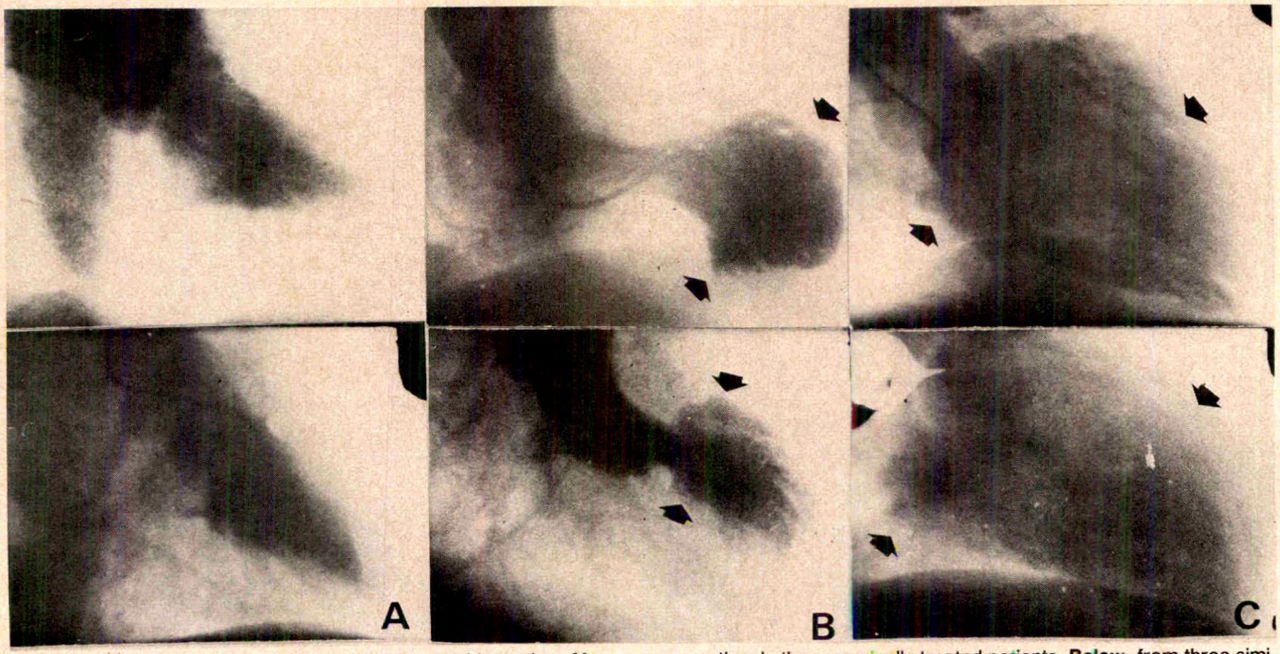

FIGURE 1. Ventriculograms (at end-systole) in unstable angina. **Above,** preoperative, in three surgically treated patients. **Below,** from three similar patients treated medically. **A,** normal ventriculogram. **B,** ventricular aneurysm. **C,** generalized hypokinesia.

TABLE VI

Angiographic Index in Subgroup of Patients

	Points*	t	P
A. Intermediate syndrome			
No previous infarction			
Surgical treatment	12.5	0.60	>0.50
Medical treatment	13.6		
Previous infarction			
Surgical treatment	19.4	0.64	>0.50
Medical treatment	18.1		
B. Progressive angina			
No previous infarction			
Surgical treatment	12.9	0.05	>0.90
Medical treatment	12.8		
Previous infarction			
Surgical treatment	16.5	1.13	>0.25
Medical treatment	18.6		

* Average of the sum of points rated according to Table I.

changes in intraventricular conduction, usually associated with changes in heart rate; and (5) T wave changes.

Hemodynamic Studies

All patients included in this study had obstructive lesions with luminal narrowing of 70 percent or more in at least one coronary artery. The left anterior descending coronary artery was the most frequently involved (94 of 97 cases) (Table IV).

Analysis of the left ventriculograms was based on a morphologic classification related to the extent of the ventricular wall involved and the degree of functional impairment of wall motion (akinesia, hypokinesia). There were two major groups (Table V). Group A included ventriculograms that revealed essentially normal findings or only minor lesions of wall motion. Group B included all ventriculograms demonstrating findings usually associated with a poor prognosis (akinesia, widespread dyskinesias, manifest hypokinesia of two walls, and the like). Almost all patients with previous infarction had obstructive lesions in at least two main coronary arteries, and their ventriculograms showed more ventricular wall damage than those of patients without infarction (Tables IV and V).

Finally, the hemodynamic data were examined together with the follow-up index described, and graded in relation to the mean for each group (Table VI). These results indicated no significant differences among the groups examined. Figure 1 illustrates three different left ventriculograms of patients with and without surgical treatment.

Excluded Patients

The need for this category indicates the importance of performing hemodynamic studies in research projects similar to ours. Table VII lists the angiocardiographic findings in this group. On the basis of these findings we excluded from surgery 10 patients

TABLE VII

Excluded Patients

Cause		Patients (no.)
A. Insufficient angiographic lesions		10
Single lesions of left circumflex artery	4	
Subaortic stenosis	2	
Aneurysm of coronary artery	1	
Hyperthyroidism and coronary spasm	1	
Normal coronary arteries	2	
B. Excessively severe angiographic lesion		5
C. Refused study		7
D. Other causes		9
Total		31

TABLE VIII

Mortality

	Patients (no.)	Mortality no.	Mortality %	χ^2	P
A. Intermediate syndrome					
Surgical treatment	24	2	8.5	4.09	<0.045
Medical treatment	20	7	35.0		
B. Progressive angina					
Surgical treatment	33	2	6.0	0.025	>0.87
Medical treatment	20	1	5.0		

with "insufficient" angiographic lesions and 5 patients whose demonstrable coronary disease was considered unsuitable for operation with use of the coronary bypass technique. In two cases, coronary arteriography demonstrated no coronary arterial alterations. In one, the patient had a uniform widespread diminution in the caliber of all coronary arteries and normal ventriculographic findings. In the other—a typical instance of progressive angina in a 44 year old man—the patient had marked electrocardiographic changes during episodes of severe pain and was studied twice by cineangiography to rule out errors in interpretation of the first film. A myocardial biopsy specimen showed only a striking increase in perinuclear lipofucsin-type pigment, as is seen in advanced cases of "senile heart."

Seven patients were excluded because they refused surgery. We excluded nine patients for "other" causes. Seven of these had a myocardial infarction between admission and definite inclusion in the study (two of these patients died). Two others,[5] permanent residents of a foreign country, experienced foreseen difficulties in remaining in the follow-up program.

Follow-Up Study

The average follow-up period of 8.3 months was not long enough to make definitive conclusions. In considering mortality rate (Table VIII), we grouped together patients with and without a previous infarc-

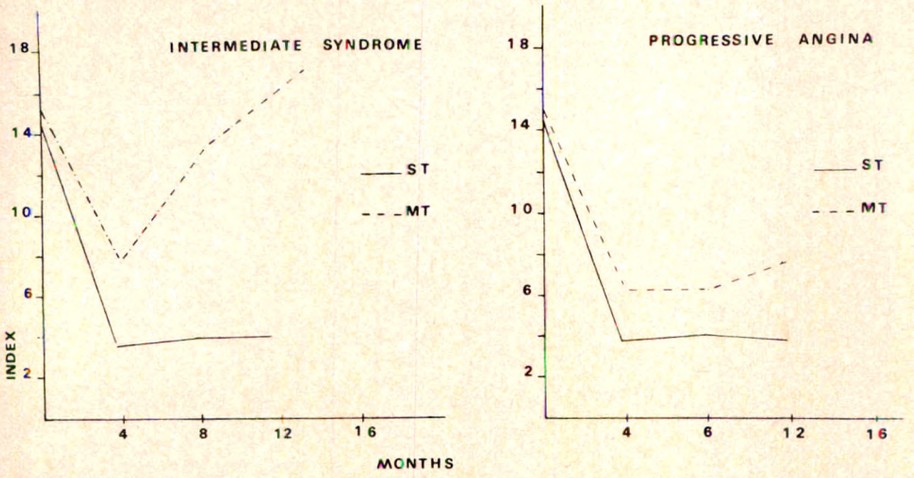

FIGURE 2. Clinical behavior of survivors after a year, in relation to the follow-up index (Table II). MT = medical treatment; ST = surgical treatment.

tion because of the small number of cases followed up for 1 year. In future studies, these two groups will be analyzed separately. Among patients with the intermediate syndrome, there was a statistically significant difference in survival rates with medical versus surgical treatment (65 vs. 95 percent). In contrast, patients with progressive angina had similar chances of survival with either mode of treatment.

Of the 57 patients operated on, only 4 died in the immediate postoperative period. To date, no late deaths have been recorded in the surgically treated group. Of the 40 patients treated medically, only 6 died in the acute period of their first hospitalization, and 2 died during the follow-up period, 8 and 6 months, respectively, after admission.

We considered of major interest an evaluation of the clinical state of the survivors. To this end, we used the index described in Table II, which grades changes in the findings of each patient examined at 4 month intervals. Figure 2 illustrates the lower scores achieved by the surgically treated patients, indicating improved clinical status.

Discussion

Classification of Patients with Unstable Angina

Unstable angina has been the subject of study since Sampson and Eliaser[3] and Feil[4] described the main clinical syndrome in 1937. Since then it has been reviewed under a variety of names: preinfarction angina,[5–7] intermediate coronary syndrome,[8,9] coronary insufficiency,[10] preinfarction syndrome,[11] premonitory symptoms of infarction,[12] unstable angina[13] and acute coronary insufficiency,[14] among others. However, we still lack reliable objective definitions that will allow grouping of patients in homogeneous categories. The need for such definitions has been emphasized by the availability of direct surgical revascularization procedures whose effectiveness must be proved or disproved.

There has also been disagreement about the true natural history of the disease. Several studies have shown a relatively good prognosis for patients with unstable angina. Fulton et al.[13] reported a mortality rate of 4 percent and a 15 percent rate of myocardial infarction. See et al.[20] recorded respective rates of 12 percent within the first year of onset, and Gazes et al.[21] followed up 40 patients with a first year mortality rate of 18 percent that 10 years later reached 40 percent. In contrast, Corday[22] reported a mortality rate of 50 percent, Beamish and Storrie[23] a rate of 60 percent and Vakil a rate of 23.7 percent with a 49.4 percent rate of infarction. These latter reports seem to indicate a high degree of risk in these patients. Since the marked discrepancies are clearly not due to faulty follow-up procedures, we must assume that each group of investigators described a population not comparable to others, perhaps because of different definitions of the patients included. Thus, our first aim was to establish clear-cut definitions that would describe as precisely as possible the subjects of our study.

We started by classifying unstable angina in three categories: the intermediate syndrome, progressive angina and postinfarction angina. To do this we drew on clinical experience gained from more than 2,000 patients admitted to our coronary care unit. Our hypothesis was that the clinical features of each group are different and are probably related to a different natural history. We excluded cases of angina of recent onset and angina of the Prinzmetal type.

The definition of the intermediate syndrome excluded patients with severe "pump failure." We believe that it is very rare to find shock or severe cardiac failure in association with an intermediate syndrome. Both occur rather frequently in subendocardial infarction, and to disregard this difference can be confusing during the first few hours of treatment.

We further subdivided each group of patients into those with and without previous myocardial infarction. Our preliminary data on the severity of coronary disease and the damage to ventricular wall motion seem to justify such a subdivision.

It is probably time to question the view of Blumgart et al.[25] in 1940 and Proudfit et al.[26] in 1967 that all patients with coronary disease have similar arterial lesions. Even if this hypothesis is true, we believe that clinical and physiopathologic behavior patterns allow the recognition of types of coronary disease of quite different evolutionary patterns and prognoses.

The protocol used in our study is complex, but we found no way to simplify the procedure. Our first problem was the decision to assign the therapeutic programs on a random basis. Our justification for making this difficult decision was that we honestly did not know at the start of the research program which group would be benefited or which would stand at a disadvantage. Furthermore, in daily practice a physician not totally convinced of a therapeutic measure often has to make a decision that later gives rise to serious doubts. We did not encounter the problem mentioned by Kayser,[27] that patients denied surgery would be lost to study because they would try to have surgery performed elsewhere. To date we have not lost a single medically treated patient to the follow-up study.

We agree with much of Kayser's description of the problems posed by a study of patients such as these. All methods used—random assignment of therapy, use of patients who refuse surgery as controls, individual preoperative or postoperative evaluation, study of patients with occluded grafts, or comparison of large groups—have important drawbacks. However, to study the features of acute coronary disease in which we are interested, the only method possible seems to be an analysis of carefully controlled small groups.

At the second stage of Phase A, a hemodynamic study was performed. Begg et al.[28] showed that the method could be used in acute cases, and we have not had any accidents due to the procedure. It may seem unnecessary to perform coronary arteriography on patients who will not be operated on. However, our findings indicate that any grouping of patients is valueless without angiographic evaluation. A research project such as ours cannot include as controls those patients without coronary disease or with minimal lesions, and there is no point in considering others with such severe disease as to contraindicate surgery. Even the most careful clinical selection will contain an error of approximately 10 percent. Of the 142 patients studied, 10 had minimal or no coronary disease, and 5 had extreme involvement; these findings created the need for a group of "excluded" cases.

The statistical comparison between patients who did and did not undergo operation revealed no significant differences on the basis of the data examined: age, clinical history, risk factors, coronary disease and ventriculograms. This requisite is essential to evaluate in the future the long-term prognosis of the disease. To this end we designed two indexes, one to gauge and compare the severity of coronary lesions and the ventriculograms, and the other to evaluate the evolution of survivors. Both indexes appear to be useful and valid.

Preliminary Results of Controlled Study

Long-term results undoubtedly require a longer follow-up period. At present we comment only upon some initial findings that have impressed us. First, it is apparent that there are important differences in the natural history of the intermediate syndrome and progressive angina, so that two separate clinical entities can be recognized that probably warrant a different therapeutic approach.

Second, as far as we can determine, mortality is significantly reduced after surgery in patients with the intermediate syndrome, and those surviving to date are in a better clinical condition. Nevertheless this result should be viewed with caution until the necessary time elapses to permit separate analysis of patients with and without previous infarction. We found no differences in mortality rates between medically and surgically treated patients with progressive angina, but a longer follow-up period is certainly warranted.

In the final stages of preparation of this manuscript our attention was drawn to an abstract on the same subject, by Théroux and Campeau.[29] These authors also found a difference in the natural history of the intermediate syndrome and progressive angina, and suggested the possibility of different therapeutic approaches. We do not know the method followed in their study, but it is interesting that their results seem essentially similar to ours.

Our purpose has been to demonstrate the feasibility of a strictly controlled study, and to find precise definitions valid enough to allow separation of homogeneous groups that can then be compared with each other. The use of indexes can be useful to this end. We expect that the continuation of our study will permit increasingly valid conclusions in due time.

Addendum

Since this paper was submitted for publication further cases were included in the study, up to March 31, 1973. The total number is now 162 patients, of whom 51 had the intermediate syndrome, 61 had progressive angina and 17 had postinfarction pain. In addition 33 other patients were excluded for the reasons given. The enlarged subgroups retain their original characteristics, and the results to date (July 1973) follow the pattern described.

Acknowledgment

Dr. René Favaloro and his team operated on these patients and the Department of Cardiovascular Disease and Cardiac Laboratory under Dr. Luis M. de la Fuente contributed valuable information. Dr. Luis Becú contributed significantly in the programming, discussion and development of our work, Professor Enrique Blaksley painstakingly reviewed the statistical analysis.

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Right Ventricular Infarction

Clinical and Hemodynamic Features

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Six patients with acute myocardial infarction presented with hemodynamic evidence of predominant right ventricular failure, characterized by a mean right atrial pressure averaging 20.2 mm Hg and left ventricular filling pressure averaging 16.3 mm Hg. Autopsy in two cases revealed extensive involvement of the right as well as the left ventricle. Clinically the patients usually had evidence of diaphragmatic wall infarction, distended neck veins, hypotension and heart block. Pressure contours and mean pressure often showed no significant change as the catheter was advanced from the right atrium to the pulmonary artery. Shock in three patients was effectively treated with plasma volume expansion, to increase further right-sided pressure, or the administration of sodium nitroprusside, to reduce left-sided filling pressure. It is suggested that when right ventricular infarction accompanies left ventricular infarction, a unique clinical and hemodynamic syndrome occurs because the ability of the right ventricle to maintain adequate left ventricular filling is impaired. Recognition of this syndrome is vital if appropriate therapy is to be instituted.

Coronary artery disease usually involves the left ventricle, and acute myocardial infarction is almost always associated with hemodynamic evidence of predominant left ventricular dysfunction.[1] Although the right ventricle may be involved in a sizable proportion of patients dying with myocardial infarction,[2,3] the lesion is usually accompanied by left ventricular infarction. Isolated infarction of the right ventricle has been noted in less than 3 percent of autopsies revealing myocardial infarction.[2]

Little attention has been devoted to the circulatory events that might accompany infarction of the right ventricle. Since the studies of Starr and his associates[4] in 1943, it has generally been assumed that right ventricular damage does not significantly impair cardiac function. The circulatory failure that has been noted to complicate right ventricular infarction in a few autopsy cases has been attributed either to low input-output failure of the left ventricle[5] or to coexisting disease of the left ventricle.[6] Hemodynamic data in these patients have not been described.

While performing studies in patients with acute myocardial infarction we found six subjects with evidence of predominant dysfunction of the right ventricle. Two of these patients died with shock, and autopsy revealed extensive infarction of this chamber. These observations suggest that infarction of the right ventricle may result in a unique clinical syndrome. Since appropriate therapy for heart failure and shock complicating right ventricular infarction may be different from that for left ventricular infarction, differentiation is of considerable clinical importance. This report describes the clinical and hemodynamic findings that appear to be characteristic of infarction involving the right ventricle and offers an explanation for the observed heart failure.

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TABLE I

Clinical and Hemodynamic Data in Six Patients with Right Ventricular Infarction

Case no.	Age (yr)	ECG	Chest X-ray	Cuff BP (mm Hg)	Pressures (mm Hg)					CI	Complications
					RA	RV	PA	PC	LVEDP		
1	63	DMI	Lungs clear	90/70	(16)	...	...	...	8	2.3	Complete heart block; shock despite dextran infusion; died
2	63	AMI	Pulmonary congestion	70/60	(18)	...	...	...	16	1.3	Complete heart block; shock; died
3	49	DMI	Pulmonary congestion	90/60	(28)	37/22	38/30 (32)	(28)	...	2.0	Frequent PVCs; survived
4	48	DMI	Lungs clear	90/60	(21)	30/19	30/19 (22)	(17)	...	2.6	Shock treated with nitroprusside; complete heart block; pacemaker; survived
5	52	DMI	Lungs clear	90/70	(20)	28/16	28/18 (22)	(16)	...	...	Shock treated with dextran; second degree heart block; pacemaker; survived
6	55	DMI	Lungs clear	80/60	(18)	30/15	30/15 (18)	(13)	...	...	Shock treated with dextran; complete heart block; survived

Figures in parentheses indicate mean pressures.

AMI = anterior wall myocardial infarction; BP = blood pressure (mm Hg); CI = cardiac index (liters/min per m²); DMI = diaphragmatic wall myocardial infarction; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary arterial; PC = pulmonary capillary wedge; PVCs = premature ventricular contractions; RA = right atrium; RV = right ventricle.

Methods

Hemodynamic studies were carried out as part of the clinical management of patients with acute myocardial infarction admitted to the intensive care unit of the Washington, D.C. Veterans Administration Hospital. Written consent for the procedures was obtained after the patients were informed of the nature and purpose of the studies. The diagnosis of myocardial infarction was based on a history of acute chest pain accompanied by electrocardiographic evidence of myocardial injury or loss of forces and a typical pattern of elevated serum enzyme values. Studies were performed as soon as possible after hospitalization of the patient, usually within 24 hours of the onset of symptoms of acute myocardial infarction.

Left ventricular filling pressure was measured either as left ventricular end-diastolic pressure obtained by retrograde left ventricular catheterization[7] or as occluded pulmonary arterial pressure obtained by floating a balloon-tipped (Swan-Ganz) catheter into the pulmonary artery. Right ventricular filling pressure (mean right atrial or right ventricular end-diastolic pressure) was measured from a catheter advanced percutaneously from an antecubital or femoral vein. Pressures were recorded on a direct-writing Hewlett Packard recorder using Statham P23Db transducers positioned at the mid-chest. Cardiac output was determined by the indicator-dilution technique using indocyanine green dye and a Gilford or Waters cuvette densitometer. Withdrawn blood was reinfused after each output determination.

Results

The simultaneously measured right and left ventricular filling pressures in 78 patients with acute myocardial infarction are plotted in Figure 1. In 72 patients, left ventricular filling pressure (average 23.0 mm Hg) was greater than right ventricular filling pressure (average 10.1 mm Hg); in 6 patients, right ventricular filling pressure (average 20.2 mm Hg) was equal to or greater than the simultaneously measured left ventricular filling pressure (average 16.3 mm Hg). The ratio of right to left ventricular filling pressure averaged 0.47 ± 0.17 (standard deviation) in the 72 patients in the former group and 1.33 ± 0.36 in the 6 patients in the latter group ($P < 0.001$).

Clinical and hemodynamic observations in the 6 patients with predominant right ventricular dysfunction are outlined in Table I. None had symptoms or signs of primary pulmonary or pulmonary vascular disease or valvular heart disease. Patient 3 had had a previous myocardial infarction and had been treated with digitalis and diuretic agents for mild symptoms of congestive heart failure.

Clinical Observations

Three patients (Cases 3, 5 and 6) were admitted within 6 hours of the onset of typical substernal chest pain. Patient 4 was transferred from another hospital 18 hours after the appearance of symptoms of acute myocardial infarction. Patient 2 presented with the complaint of insidious weakness accompanied by mild chest pain during the previous 3 days. Patient 1

experienced shock 10 days after experiencing an acute myocardial infarction treated at another hospital.

All six patients had low auscultatory blood pressure on admission, including Patients 3 and 5 who gave a history of untreated hypertension before their acute illness (Table I). In five patients the diagnosis of shock was made on the basis of cool, clammy skin, disturbed sensorium, oliguria, or all three. Patient 3 had no signs of impaired peripheral blood flow and his arterial pressure increased spontaneously within the first 12 hours after hospitalization.

All six patients had marked systemic venous engorgement without orthopnea or significant shortness of breath. Chest X-ray film at the time of admission revealed clear lung fields in four patients and evidence of moderate pulmonary congestion in the other two.

Electrocardiogram

Five patients had electrocardiographic findings compatible with acute diaphragmatic wall infarction (Table I). In Patient 2, the electrocardiogram was consistent with anterolateral infarction.

Four patients had complete heart block, and one had second degree block within the first 24 hours after admission to the intensive care unit. Patient 1 died before normal rhythm could be restored; in Patient 6, administration of atropine and small doses of isoproterenol maintained an adequate ventricular rate until the block cleared. In the other three patients with block, a transvenous pacemaker was utilized to control ventricular rate for 48 to 72 hours.

Hemodynamics

Mean right atrial pressure was markedly elevated to levels ranging from 16 to 28 mm Hg (Table I). In two patients left ventricular catheterization revealed normal or only slightly increased left ventricular end-diastolic pressure. In the other four patients the pulmonary artery was catheterized. Systolic right ventricular and pulmonary arterial pressures were within the normal range, and pulmonary arterial diastolic and wedge pressures were only minimally increased in three patients. Patient 3 had the highest value for pulmonary wedge pressure (28 mm Hg), but even in this patient the left ventricular filling pressure was no greater than the mean right atrial pressure.

The demonstration of preponderant right ventricular failure in a patient with shock is highly suggestive of acute pulmonary embolization.[7] This diagnosis was suspected in Patients 1 and 2, who did not undergo bedside pulmonary arterial catheterization. Indeed, Patient 1 died in the catheterization laboratory while he was being prepared for emergency pulmonary arteriography. No pulmonary emboli were found at autopsy in either of these patients.

In the other four patients pressures recorded from the pulmonary artery revealed that the defect was not increased pulmonary vascular resistance but rather impaired pressure generation by the right ventricle. The mean level of pulmonary arterial pressure averaged only 2 mm Hg more than mean right atrial pressure. In three patients (Cases 4, 5 and 6), the contour of the pressure pulses remained practically identical as the catheter was advanced from the right atrium to the pulmonary artery. This finding produced some confusion during the blind catheterization with the balloon-tipped catheter, and it was necessary in each instance to document the location of the catheter by fluoroscopy or X-ray film. In Patient 4 repeat studies the following day in the catheterization laboratory using fluoroscopy and a Cournand catheter yielded identical results (Fig. 2).

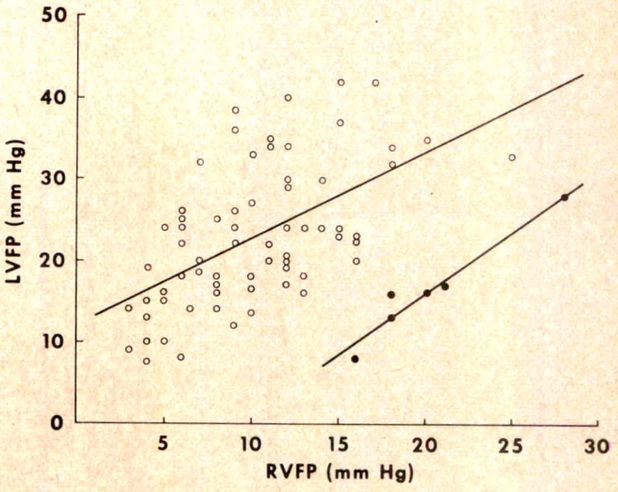

FIGURE 1. Simultaneous right ventricular filling pressure (RVFP) (mean right atrial or right ventricular end-diastolic pressure) and left ventricular filling pressure (LVFP) (left ventricular end-diastolic pressure or mean pulmonary wedge pressure) in patients with acute myocardial infarction. **Open circles** represent values in 72 patients with predominantly increased left ventricular filling pressure; **dots** represent 6 patients with predominantly increased right ventricular filling pressure. Regression lines for the two groups have been drawn.

Cardiac output, measured in four patients, was reduced in three and within the normal range in Patient 4. In Patients 1, 3 and 4, the hypotension seemed to be disproportionate to the modest reduction in cardiac output, and calculated total systemic vascular resistance was not elevated above normal levels.

Management of Shock

Because of the normal or near-normal left ventricular filling pressures, Patients 1, 5 and 6 were treated with rapid infusion of dextran, which increased arterial pressure and reduced the signs of impaired peripheral blood flow. Shock was corrected in Patients 5 and 6 but not in Patient 1, although cardiac index in this patient was increased to 2.5 liters/min per m^2. In Patient 4 shock was treated with an infusion of sodium nitroprusside which resulted in a marked improvement in peripheral blood flow.[8] In Patient 2 ar-

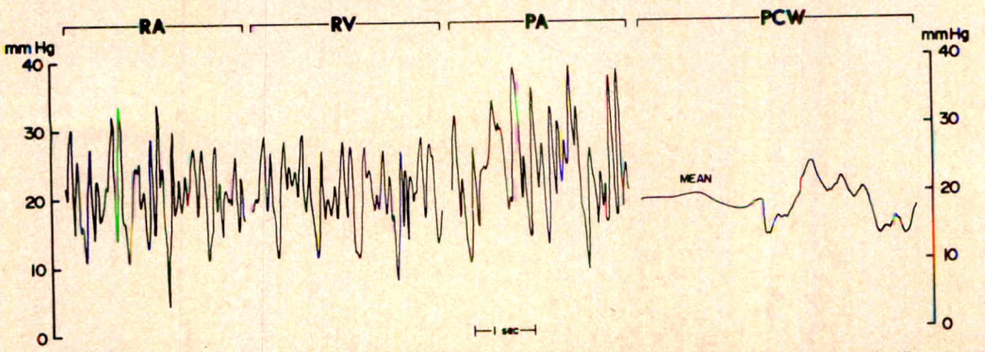

FIGURE 2. Case 4. Pressure tracings recorded on the second day of hospitalization as the catheter was guided under fluoroscopic control from the right atrium (RA) to the pulmonary arterial wedge position (PCW). Pressure fluctuations in the right ventricle (RV) and pulmonary artery (PA) were not synchronous with ventricular systole and probably represent the transmission of atrial pressure waves into the pulmonary artery through a noncontracting right ventricle.

terial pressure was maintained for approximately 24 hours with infusion of metaraminol, but the signs of shock were not corrected and he died. This patient was treated in 1969 before we understood the therapeutic implications of right ventricular infarction.

Autopsy Findings

Autopsy in Patient 5 revealed complete occlusion of the right coronary artery with extensive infarction of the posterior wall of the right ventricle, right atrial appendage and interventricular septum with extension to the posterior wall of the left ventricle. Mural thrombus was found in the right atrium and right ventricle. There was fibrinous pericarditis. Patient 2 had extensive disease involving all three coronary arteries with old and recent infarctions of the lateral wall of the left ventricle and patchy infarction involving most of the right ventricle. Mural thrombus was present in the right ventricle. No pulmonary emboli were identified in either patient.

Clinical Course

The four survivors had a relatively benign hospital course after the shock and rhythm disturbances cleared. All were able to walk without discomfort and were relatively asymptomatic at the time of discharge.

Patient 3 was recatheterized 3 weeks after his acute myocardial infarction. Mean right atrial pressure was reduced to 7 mm Hg, pulmonary arterial diastolic pressure was 14 mm Hg and pulmonary wedge pressure 9 mm Hg. The mean pulmonary arterial pressure was 18 mm Hg, so that the right ventricle was generating a mean pressure of 11 mm Hg compared to 4 mm Hg at the time of the first study. Cardiac index had increased only slightly to 2.2 liters/min per m^2. In Patient 4, right heart catheterization also was repeated 3 weeks after the first study, but the pulmonary artery was not entered. Mean right atrial pressure was 10 and right ventricular pressure was 20/12 mm Hg.

Discussion

Myocardial infarction involving the right ventricle has previously been diagnosed only at autopsy. Most of the reported infarcts have involved the posterior wall of the right ventricle, septum and adjacent left ventricle; they have usually been associated with occlusion of the main right coronary artery; and the electrocardiograms usually have been typical of posterodiaphragmatic wall infarction.[5,6,9] Occasionally, focal infarcts of the anterior wall of the right ventricle have been accompanied by electrocardiographic abnormalities consistent with anterior wall injury.[6] The circulatory failure observed in these fatal cases of right ventricular infarction has been attributed most often to involvement of the septum and left ventricle.[6] Thus, no specific circulatory pattern of right ventricular infarction has been recognized.

The six cases described here may represent the first instances of antemortem clinical diagnosis of right ventricular infarction. All patients presented with hemodynamic evidence of right ventricular failure disproportionate to left ventricular failure, an unusual finding in patients with acute myocardial infarction.[1] Catheterization data revealed that the right ventricle was generating very little pressure, and in three patients the pulmonary arterial tracing was nearly identical to that in the right atrium. Although right ventricular infarction could be documented anatomically only in the two patients who died, the typical clinical, electrocardiographic and hemodynamic features in the four survivors make it likely that these patients also had infarctions involving the right ventricle.

The absence of pressure generation by the right ventricle in these patients is reminiscent of the chronic right ventricular failure associated with Uhl's anomaly (parchment heart), in which the right ventricular myocardium is aplastic.[10,11] The transmission of right atrial *a* waves directly into the pulmonary artery without alteration by the right ventricle has been described both in patients with this syn-

drome[11,12] and in a patient with chronic right ventricular failure whose autopsy revealed extensive fibrosis of the right ventricle and a rudimentary right coronary artery.[13] The latter case may represent the chronic form of disability from right ventricular ischemic heart disease that was observed in its acute phase in our six patients.

Clinical features: The typical clinical features in our cases were electrocardiographic evidence of acute diaphragmatic wall infarction accompanied by hypotension and prominent venous engorgement complicated by the development of complete atrioventricular block. The heart block undoubtedly represents involvement of the region of the atrioventricular node supplied by the right coronary artery.[14] Previous human autopsy studies[6] and recent experimental data[15] have indicated that right ventricular infarction occurs only when the right ventricle is the site of preexisting hypertrophy. However, our patients had no signs or symptoms suggestive of previous right ventricular or pulmonary vascular disease although Patient 3 had had mild congestive heart failure.

It is unlikely that infarction was confined to the right ventricle in any of our patients. The only patient with a normal left ventricular filling pressure had autopsy evidence of infarction extending to the posterior wall of the left ventricle. In the other patients, left ventricular filling pressure (pulmonary wedge or left ventricular end-diastolic pressure) was slightly to moderately increased. Despite the presence of these features consistent with impairment of left ventricular function, right ventricular failure seemed to dominate the clinical findings. Symptoms of pulmonary congestion were absent in all six patients, and the lung fields were clear radiographically in four. Mean right atrial pressure was greater than left ventricular filling pressure in five patients and identical to left ventricular filling pressure in the patient with a history of previous myocardial infarction and chronic heart failure.

Hemodynamic consequences of right ventricular infarction and their treatment: The hypotension and reduced cardiac output in these patients could be attributed to inadequate left ventricular filling. In five patients the level of left ventricular filling pressure was below the 20 to 25 mm Hg range previously noted to provide optimal cardiac output in patients with left ventricular infarction.[16,17] In patients with normal right ventricular function, adequate pulmonary blood flow and filling of the acutely infarcted left ventricle usually can be maintained with only a slight increase in right atrial pressure.[1] However, when right ventricular contraction is severely impaired, as it apparently was in our patients, filling of the left ventricle is dependent on distension of the right atrium or right ventricle. Left ventricular filling could then be supported by any of these possible mechanisms: (1) increased right ventricular end-diastolic volume, which could augment contractile force of the residual functioning fibers in the damaged right ventricle; (2) increased right atrial contractile force, which might help to propel blood into the pulmonary artery in the absence of right ventricular contraction; or (3) passive flow along a right atrial-left atrial pressure gradient through the low resistance pulmonary vascular bed.[18] A similar modification of the pressure gradient to favor left ventricular filling could be accomplished if left atrial pressure were reduced to a greater extent than right atrial pressure.

These hemodynamic principles were utilized in selecting therapy for shock in four of our patients. Rapid intravenous infusion of dextran in three patients increased both right and left ventricular filling pressures and was thus effective in partly or completely restoring adequate arterial pressure and peripheral blood flow. In one patient shock was corrected by infusion of the vasodilator sodium nitroprusside, which increases systolic emptying of the left ventricle by reducing impedance to aortic flow.[8] The reduction of left atrial pressure during nitroprusside infusion therefore encourages enhanced inflow and increased cardiac output. The hemodynamic data and response to therapy in these patients are consistent with the hypothesis that they had left ventricular ischemic damage, causing a modest increase in left atrial pressure, perhaps in part because of a decrease in left ventricular compliance.[1,17] This left ventricular dysfunction probably would not in itself have precipitated circulatory failure but, because of the concomitant right ventricular damage, the right ventricle did not generate enough pressure to maintain optimal left ventricular filling in the presence of increased left atrial pressure.

Coexisting left ventricular damage may account in part for the increased central venous pressure and right ventricular failure observed in our patients in contrast to the nearly normal venous pressures noted by Starr et al.[4] after experimental right ventricular destruction. Tricuspid regurgitation due to dilation of the right ventricle or malfunction of the papillary muscles also can contribute to increased right atrial pressure. Nonetheless, the predominant right ventricular failure noted in our patients indicates that, contrary to the concept developed from Starr's observations, right ventricular damage produces evidence of right ventricular failure. Experimental evidence to confirm these clinical observations has been obtained in dogs studied in our laboratory.[19] However, unlike our patients, dogs subjected to massive destruction of the right ventricle may maintain nearly normal right ventricular and pulmonary arterial pressures.[19–21] It is not known whether these contrasting findings result from species differences, the effect of different modes or anatomic site of insult to the right ventricle, or the effect of concomitant left ventricular damage in our patients.

Prognosis: Although two patients with right ventricular infarction died with shock, three of the four survivors recovered from shock. This survival rate of 60 percent is considerably higher than we[1] and others[22] have reported in shock complicating left ven-

tricular myocardial infarction. Furthermore, studies repeated in two of these patients 3 weeks after the acute right ventricular infarction revealed that right-sided pressures had returned almost to normal. Patients with left ventricular infarction usually do not have normal left-sided pressures when restudied 3 weeks after infarction.[17] These observations suggest that the syndrome of shock that accompanies right ventricular infarction may be associated with less irreversible myocardial damage than shock accompanying left ventricular infarction. Data are not yet adequate to determine whether the hemodynamic improvement noted during convalescence represents recovery of right ventricular function or is the consequence of a passive reduction in right ventricular pressure due to a decrease in left ventricular filling pressure.

Incidence: The incidence of hemodynamically significant right ventricular infarction cannot accurately be assessed from our data. The patients with acute myocardial infarction submitted to study were not unselected, but rather represented primarily those with evidence of more severely disturbed cardiac performance. Since increased venous pressure, which was characteristic of the patients with right ventricular infarction, was one criterion used in selecting subjects for study, our data may overestimate the frequency of right ventricular involvement. Furthermore, the relation between predominant right ventricular failure and anatomic evidence of infarction of the right ventricle is unknown. Nonetheless, the 8 percent prevalence of right ventricular infarction based on hemodynamic observations in our study is not too dissimilar from the 14 percent prevalence of right ventricular involvement noted in previous autopsy studies[2] of patients with acute myocardial infarction.

Clinical management: Clinical recognition of right ventricular infarction may be important in patient management. Right ventricular infarction should be considered in any patient with an acute diaphragmatic wall infarction and evidence of systemic venous engorgement. Left ventricular or pulmonary arterial catheterization should be performed in such patients to document the severity of left ventricular dysfunction. Although the presence of distended neck veins in a patient with acute myocardial infarction is usually considered a contraindication to volume expansion, rapid infusion of dextran may reverse shock in these patients if left ventricular filling pressure is less than 20 mm Hg. If filling pressure is increased and if arterial pressure has not fallen to hypotensive levels, cautious administration of a vasodilator drug may reduce left atrial pressure and thus increase pulmonary flow.[8] Mechanical assist devices are now being used to manage shock complicating acute myocardial infarction, and counterpulsation with an intraaortic balloon could theoretically augment cardiac output by reducing left ventricular filling pressure even when right ventricular failure predominates. However, the technique is likely to be less effective than when it is used in massive left ventricular infarction, and our findings suggest that shock associated with right ventricular infarction may respond to less drastic measures.

Acknowledgment

We acknowledge the technical assistance of Eleanor Garlisi, RN and Helen Firmin, RN and the secretarial assistance of Miss Santa Ferraro.

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Electrocardiographic and Serum Enzyme Changes of Myocardial Infarction After Coronary Artery Bypass Surgery

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Serial preoperative and postoperative electrocardiograms were obtained in 50 patients undergoing coronary artery bypass surgery, 15 undergoing aortic valve replacement and 13 undergoing mitral valve surgery. Postoperative infarction was defined as the appearance of new Q waves on the postoperative electrocardiogram. Infarction occurred in 5 of 50 patients (10 percent) who underwent coronary artery bypass surgery. Age, preoperative hypertension or a pattern of left ventricular hypertrophy on the electrocardiogram did not correlate with infarction. Coronary disease was more severe in patients with than in those without infarction (mean of 3.2 vessels with 50 percent stenosis compared to 2.4 vessels). There was no correlation with bypass time or use of cross-clamping of the aorta during surgery. Postoperatively, 4 of 5 patients (80 percent) with infarction had serum values for glutamic oxaloacetic transaminase (SGOT) and creatine phosphokinase (CPK) of more than 200 and more than 2,000 international units, respectively, whereas 3 of 45 (7 percent) without infarction had this pattern ($P < 0.001$).

Of patients undergoing aortic valve replacement, 3 of 15 (20 percent) had postoperative infarction. All 3 of these patients had a serum glutamic oxaloacetic transaminase value of more than 200 and a creatine phosphokinase value of more than 2,000 units, compared to 2 of 12 (17 percent) without infarction. None of the 12 patients who underwent mitral valve surgery had postoperative infarction, and none had a serum glutamic oxaloacetic transaminase value of more than 200 or a creatine phosphokinase value of more than 2,000 units.

Myocardial infarction after coronary artery bypass surgery is more likely in patients with at least three-vessel disease but appears to be unrelated to pump time or aortic cross-clamping. Localized snaring or clamping of coronary arteries may be important. Postoperative serum glutamic oxaloacetic transaminase and creatine phosphokinase levels correlate with electrocardiographic evidence of infarction.

The rate of postoperative electrocardiographic evidence of infarction after internal mammary artery implantation into the myocardium has been reported to be about 20 percent.[1–4] Several recent reports have shown a similar rate of infarction pattern after coronary artery bypass surgery.[5–9] Although it has been shown that serum glutamic oxaloacetic transaminase (SGOT) and creatine phosphokinase (CPK) correlate with electrocardiographic evidence of infarction postoperatively, a recent communication[6] stresses the need for determination of creatine phosphokinase isoenzyme levels for accurate diagnosis of infarction.

This report describes a prospective study of 78 patients undergoing coronary bypass and valvular surgery. Evidence of infarction and other postoperative electrocardiographic changes are described in detail. Pre- and postoperative variables thought to be important in the

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TABLE I

Electrocardiographic Changes After Coronary Artery Bypass, Aortic Valve Replacement and Mitral Valve Surgery

	CAB (50 patients)	AVR (15 patients)	MVS (13 patients)
Infarction	5	3	0
No change	13	4	6
T wave change	20	4	6
S-T segment change	6	2	1
Decreased R wave*	4	3	0
Deeper or wider Q wave*	4	0	0
Notching QRS	3	0	0
Transient QRS change	2	1	0
Axis shift: LAH, LPH	1	0	0
LBBB	0	0	1
RBBB	0	1	0
Miscellaneous	2	1	0

* One lead.

AVR = aortic valve replacement; CAB = coronary artery bypass; LAH = left anterior hemiblock; LBBB = left bundle branch block; LPH = left posterior hemiblock; MVS = mitral valve surgery; RBBB = right bundle branch block.

origin of infarction are evaluated, and postoperative electrocardiographic changes are compared with serum levels of glutamic oxaloacetic transaminase and creatine phosphokinase.

Methods

Preoperative and serial postoperative electrocardiograms were obtained in a consecutive series of patients undergoing operation by two cardiac surgeons at University Hospital from July 1972 to December 1972. Of 50 patients undergoing coronary artery bypass two had aortic valve replacement in addition. Of the 15 patients with aortic valve replacement, 4 had combined aortic and mitral valve surgery and 1 had repair of a ventricular septal defect. Twelve patients had mitral valve surgery and one had ventricular aneurysmectomy. For analysis, the latter patient is included in the group with mitral valve surgery.

Anesthesia was induced with thiopental sodium and succinylcholine chloride and subsequently maintained with halothane. Perfusion was at a flow rate of 2.25 liters/m^2 body surface area, temperature 30° to 34° C, using a Pemco roller pump and a Bentley disposable bubble oxygenator. The patients were heparinized with 300 units of heparin/kg body weight. The pump oxygenator was primed with 2,000 ml of Ringer's lactate solution and 1,000 to 1,500 ml of citrated blood. The pH of the citrated blood was adjusted to 7.4 with tromethamine (THAM®). In addition, 0.6 g of calcium chloride was given for each 500 ml of citrated blood, and 1 g of magnesium sulfate and 10 mEq of potassium chloride were added; 12.5 g of 50 percent glucose was added to the oxygenator.

Patients undergoing coronary bypass procedures either had electrically induced fibrillation with no aortic cross-clamping or intermittent aortic cross-clamping at 30° followed by 3 to 5 minutes of coronary perfusion. During aortic valve replacement, coronary perfusion was performed with silastic coronary cannulas at total flow rates of approximately 300 cc/min. Coronary perfusion was carried out for 3 to 5 minutes followed by ischemic periods of 10 to 15 minutes. Perfusion temperatures were 30° to 32° C.

Postoperative electrocardiograms were obtained on postoperative days 1 through 3, and then every several days until a stable pattern was noted. Tracings were obtained at least 1 week postoperatively in all patients. The tracings were evaluated independently by two of us. The criterion for definite transmural infarction was a Q wave not present

TABLE II

Coronary Artery Bypass Surgery: Preoperative and Operative Variables

Variables	No Infarct (45 patients)	Infarct (5 patients)
Preoperative Variables		
*Mean age (yr)	56	52
*Sex	34M, 11F	5M
*Infarct on electrocardiogram	16 of 45	3 of 5
*Hypertension	11 of 45	0
*Left ventricular hypertrophy on electrocardiogram	2 of 45	0
Operative Variables		
Mean pump time (hr)	2.6	2.98
Pump time >3 hours	19 of 45	2 of 5
Aortic clamping	24 of 45	2 of 5
Mean clamping time (min)	32.2	10.5
Aortic clamping >15 minutes	13 of 24	0
Bypass grafts (mean no.)	2.4	3
Three or more grafts	27 of 45	5 of 5

* Differences not significant.

TABLE III

Coronary Artery Bypass Surgery: Distribution and Severity of Coronary Artery Disease

	No Infarct (45 patients)	Infarct (5 patients)
Coronary arteries with >50% stenosis (no.)*		
1	5 of 45	0
2	9 of 45	0
3	25 of 45	4 of 5
4	6 of 45	1 of 5
Mean	2.7†	3.2†
Distribution of coronary arteries with >50 % stenosis		
Main left coronary artery	3 of 45	0
Left anterior descending artery	38 of 45	4 of 5
Left circumflex artery	32 of 45	4 of 5
Right coronary artery	31 of 45	3 of 5
Patients with >50% stenosis of 3 or more arteries	31 of 45†	5 of 5†

* Main left, right coronary, left anterior descending and left circumflex coronary arteries.

† Differences not significant.

preoperatively of more than 0.04 second's duration, with or without corresponding S–T segment changes in one or more leads, and, for probable transmural infarction, a marked loss of R voltage in two or more leads without evidence of conduction block. S–T segment changes were not accepted as evidence for infarction but were listed under miscellaneous changes.

Patients were classified as hypertensive preoperatively if they had a history of hypertension requiring therapy or two independent blood pressure recordings with a systolic pressure of more than 140 or a diastolic pressure of more than 90 mm Hg. A diagnosis of left ventricular hypertrophy was made if the preoperative electrocardiogram showed an S wave in lead V_2 and an R wave in lead V_5 of 35 mv or greater with corresponding S–T and T wave changes in the left precordial leads. Preoperative angiograms were reviewed by the attending cardiology staff. Operative records were reviewed for duration of cardiac bypass and aortic cross-clamping and for perfusion pressures during bypass.

Serial serum glutamic oxaloacetic transaminase and creatine phosphokinase levels were obtained on postoperative days 1 through 3 in all cases, and for longer periods as indicated. Both enzyme levels were determined with use of the SMA-Flex system. The results were evaluated statistically using either Fischer's exact method for 2 by 2 tables or Student's *t* test.

Results

Coronary Artery Surgery

Of the 50 patients in this group, 4 had definite and 1 had probable transmural infarction postoperatively (Table I). There were three anterior and two inferior wall infarctions. All five patients manifested electrocardiographic evidence of infarction on postoperative day 1, and in each a bypass graft had been placed in the area of infarction. Among the 45 patients without an infarction pattern on the postoperative electrocardiogram, various changes were noted (Table I). Twenty patients showed changes in the T vector; in 13 patients the electrocardiogram was unchanged. The other changes listed were noted infrequently. Of particular interest are the two patients who demonstrated transient loss of R wave voltage or transient Q waves. In one case included under miscellaneous QRS changes, the precordial pattern changed from one of probable anterior infarction to one of normal precordial R wave progression.

There was no difference between patients with and without infarction in relation to the following preoperative variables: electrocardiographic evidence of previous infarction or left ventricular hypertrophy or clinical evidence of hypertension (Table II). The number of coronary vessels with more than 50 percent stenosis was greater in the group with infarction (3.2 vs. 2.7 vessels, Table III), and the majority of patients in each group had at least three-vessel disease. Although the distribution of diseased vessels was similar, three patients in the group without infarction had disease of the left main coronary artery compared to none in the group with infarction (Table II).

Patients with infarction had a mean of 3 bypass grafts; those without infarction averaged 2.4 grafts. All patients with infarction had three or more grafts compared to 27 of 45 patients without infarction. Each of the five patients with infarction had a single internal mammary artery bypass to the left anterior descending coronary artery in addition to the saphenous vein bypasses to the other vessels; 21 of 45 patients without infarction had one internal mammary artery bypass to the right or left coronary artery in addition to the other grafts, and five had double mammary artery bypass procedures. There was no significant difference in the prevalence of infarction between patients with and without internal mammary artery grafts.

Although mean cardiac bypass time was slightly longer in the group with infarction, the percentage of patients in each group with a pump time of more than 3 hours did not differ. Two of five patients with infarction and more than half of those without infarction underwent aortic cross-clamping. The mean duration of clamping time was shorter in the group with infarction, and none of these patients had a cross-clamping interval of more than 15 minutes; 13 of 24 patients without infarction underwent cross-clamping for more than 15 minutes. Perfusion pressures during cardiac bypass did not correlate with postoperative infarction.

There were significant differences between the two groups in peak serum glutamic oxaloacetic transaminase and creatine phosphokinase levels for postoperative days 1 through 3 (Table IV). Four of the five patients with infarction had serum glutamic oxalo-

TABLE IV

Serum Enzyme Values After Coronary Artery Bypass, Aortic Valve Replacement and Mitral Valve Surgery

	Coronary Artery Bypass		Aortic Valve Replacement		Mitral Valve
	No Infarct (45 patients)	Infarct (5 patients)	No Infarct (12 patients)	Infarct (3 patients)	Surgery* (13 patients)
Peak CPK mean	1654 (<0.01)	4458	1929	5598	1674
no. with CPK >2000	8 of 45	4 of 5	4 of 12	3 of 3	2 of 13
Peak SGOT mean	185 (<0.05)	355	175	829	150
no. with SGOT >200	10 of 45	4 of 5	2 of 12	3 of 3	1 of 13
no. with SGOT >300	6 of 45	3 of 5	1 of 12	3 of 3	1 of 13
no. with SGOT >200 and CPK >2000	3 of 45 (<0.001)	4 of 5	2 of 12	3 of 3	0 of 13

* No patient in this group had postoperative infarction.
Figures in parentheses indicate probability values.
CPK = creatine phosphokinase (international units); SGOT = serum glutamic oxaloacetic transaminase (international units).

TABLE V

Aortic Valve Replacement: Preoperative and Operative Variables

Variables	No Infarct (12 patients)	Infarct (3 patients)
Preoperative Variables		
Mean age (yr)	54	54
Sex	9M, 3F	2M, 1F
Infarct on electrocardiogram	1 of 12	0
Hypertension	3 of 12	2 of 3
Left ventricular hypertrophy on electrocardiogram	6 of 12	3 of 3
Coronary arteries with >50 % stenosis	2 patients with 1-vessel disease	1 patient with 1-vessel disease
Operative Variables		
Mean pump time (hr)	2.6	3.2
Pump time >3 hours	5 of 12	2 of 3
Mean time of coronary ischemia (min)		
Left coronary arteries	53	66
Right coronary artery	66	84
Coronary ischemia >20 minutes		
Left coronary arteries	5 of 12	2 of 3
Right coronary artery	5 of 12	2 of 3

acetic transaminase and creatine phosphokinase values of more than 200 and more than 2,000 international units, respectively; only 3 of 45 patients without infarction had this pattern ($P < 0.001$). Of these three patients, one had no change on the postoperative electrocardiogram, and the other two demonstrated T wave changes and deeper Q waves in leads II, III and aVF. Four of the five patients with infarction required vasopressors in the immediate postoperative period for prolonged hypotension, reduced central venous PO_2 or decreased urinary output; 24 of 45 patients without infarction received this therapy. Electrocardiographic evidence of infarction was present either before or within several hours after institution of vasopressor therapy. The two postoperative deaths occurred in the group with infarction. One patient had shock postoperatively and died with acute renal and hepatic failure and the other sustained cardiac arrest 4 days postoperatively with an area of posterior infarction noted at reoperation. Death secondary to Candida albicans sepsis occurred several months later. Electrocardiographic evidence of infarction was noted before these complications occurred.

Aortic Valve Surgery

Ten patients with isolated aortic valve replacement, four with combined aortic and mitral valve surgery, and one with aortic surgery and ventricular septal defect repair are included in this group. Two patients demonstrated definite infarcts on the postoperative electrocardiogram and one evidenced a probable infarct. The other electrocardiographic changes are listed in Table I. The distribution was similar to that in patients who underwent coronary artery bypass surgery. Preoperatively, hypertension and a pattern of left ventricular hypertrophy on the electrocardiogram occurred more often in patients with infarction (Table V). Only three patients had one-vessel coronary disease. The patients with infarction tended to have longer periods of bypass pump and coronary ischemia and greater perfusion pressures than those without infarction. The small numbers in this group preclude statistical evaluation. As in the patients who underwent coronary bypass, postoperative enzyme studies separated the two groups: 2 of 12 without infarction had serum values for glutamic oxaloacetic transaminase and creatine phosphokinase of more than 200 and more than 2,000 international units, respectively, whereas all of the patients with infarction manifested this pattern. In this group, the serum levels of these enzymes were generally higher than levels in the group undergoing coronary artery bypass (Table IV).

Mitral Valve Surgery

This group comprised 12 patients with rheumatic heart disease who had mitral valve surgery and 1 patient with left ventricular aneurysmectomy. No postoperative infarctions were noted; other electrocardiographic changes are listed in Table I. One patient had left bundle branch block postoperatively. The patient with left ventricular aneurysmectomy had three-vessel coronary disease, as did the patient with mitral valve replacement who had postoperative left bundle branch block. Eleven of 13 of these patients had aortic cross-clamping during surgery but none had coronary perfusion (Table VI). Mean pump time was less than in the groups that underwent coronary artery bypass or aortic valve replacement. None of these patients had a serum glutamic oxaloacetic transaminase value of more than 200 or a creatine phosphokinase value of more than 2,000 units (Table IV).

Discussion

Several studies[1–4] have demonstrated postoperative infarction in 17 to 20 percent of patients undergoing Vineberg procedures; only new Q waves were accepted as evidence of infarction. Recent reports suggest a similar rate of infarction after coronary bypass surgery. Brewer et al.[5] reported infarction in 17 percent of 220 patients surviving operation. When autopsy studies on patients dying at operation are included, the overall prevalence was 20 percent. Dixon et al.[6] noted infarction in 20 percent of 40 patients undergoing coronary artery bypass grafting. Anderson et al.,[7] using electrocardiographic and vectorcardiographic criteria for diagnosis, reported infarction in 17 percent of 46 patients undergoing coronary artery bypass surgery. Thirty percent of 44 patients

undergoing such surgery had new Q waves in the series of Espinoza et al.[8] Finally, Friedberg et al.[9] studied pre- and postoperative vectorcardiograms in 193 consecutive patients undergoing coronary artery bypass surgery and found evidence of infarction in 8 percent.

The frequency of infarction in the 50 patients undergoing coronary artery bypass in our series was 10 percent. Because the Q wave criterion alone was used, it is possible that subendocardial infarcts, manifested only by S–T and T wave changes, may have been missed. However, all of the series noted used similar criteria and thus the results may be compared. Except for Friedberg's series,[9] the reported rate of infarction after coronary artery bypass graft surgery ranges from 17 to 30 percent. Brewer et al.[5] included changes of left bundle branch block and left anterior hemiblock in their group with infarct. Only one patient in our series had left anterior hemiblock postoperatively. Similarly, although Brewer et al. included several operative deaths with autopsy-proved infarcts in their report, only one patient in our series died during coronary bypass surgery; autopsy was not performed. Patients in our series were not excluded from operation if total occlusion of a vessel was noted on angiograms and the distal vessel was not visualized, or if distal vessels were visualized but were severely reduced in diameter. Similarly, patients with increased left ventricular end-diastolic pressure and areas of left ventricular dyskinesis were included in our group, and the majority had disease of at least two coronary arteries. Therefore, our patients were not likely to be "better risks" than others studied. The wide range in reported occurrence of postoperative infarction may be related to differences in operative technique and establishment of patent saphenous vein-coronary artery anastomoses.

TABLE VI

Mitral Valve Surgery: Preoperative and Operative Variables

Variables	No Infarct* (13 patients)
Preoperative Variables	
Mean age (yr)	52
Sex	5M, 8F
Infarct on electrocardiogram	1 of 13
Hypertension	1 of 13
Left ventricular hypertrophy on electrocardiogram	1 of 13
Coronary arteries with >50% stenosis	2 patients with 3-vessel disease
Postoperative Variables	
Mean pump time (hr)	1.3
Pump time >3 hours	0
Aortic clamping	11 of 13
Mean clamping time (min)	20.5
Aortic clamping >15 minutes	4 of 13

* No patient who underwent mitral valve surgery had postoperative infarction.

Possible causes of postoperative Q waves: The presence of new Q waves postoperatively may be related to factors other than direct damage to the myocardium or compromised coronary arteries. Chamberlain and Edmonds-Seal[10] studied the effects of general anesthesia on 217 patients with evidence of either ischemia or left ventricular hypertrophy on the preoperative electrocardiogram. All 217 patients underwent nonthoracic surgery, and new Q waves were noted in 3. Topkins and Artusio[11] studied the effect of anesthesia and general surgery on 12,054 patients with no previous history of myocardial infarction and found postoperative infarction in 0.66 percent. Of 658 patients with a prior history of infarction, 6 percent had postoperative infarction.

Kline et al.[12] noted transient Q waves in 8 of 30 patients during coronary bypass surgery and offered several possible explanations, including hypothermia, transient ischemia and localized hyperkalemia. These factors would not explain persistence of Q waves postoperatively. In our series, however, we noted transient postoperative Q waves in 2 patients and S–T and T wave changes in 26. Pericarditis in the postoperative period also might explain some of these findings.

Correlation with coronary disease, perfusion time and aortic cross-clamping: Infarction may occur after cardiac surgery in patients without significant coronary artery disease. Infarction, defined as new Q waves, was noted in 8 of a series of 126 patients[13] undergoing aortic or mitral valve surgery; infarction correlated with perfusion time but not with aortic cross-clamping. In our series, infarction was noted in 3 of 15 patients undergoing aortic valve replacement, and only 1 of these 3 had single-vessel coronary disease. Thus, coronary disease is an unlikely cause of infarction in our group. No infarctions were noted in the patients undergoing mitral valve surgery. (Although the mean cross-clamping time was shorter in this group, coronary perfusion was performed only in the group undergoing aortic valve surgery.) The critical factor may be the left ventricular hypertrophy noted in the patients undergoing aortic valve replacement. Coronary perfusion may, in some cases, be inadequate to meet the oxygen requirements of the hypertrophied left ventricle.

Brewer et al.[5] observed significant correlations between postoperative infarction and the number of bypass grafts and operative pump time. In their series the group with infarction had more extensive coronary artery disease and a slightly longer mean pump time than the group without infarction, but the differences were not statistically significant. However, the number of patients with a pump time of more than 3 hours did not differ significantly in their two groups. In addition, only 2 of 5 patients in their group with infarction underwent aortic cross-clamping, a factor thought to be important in the genesis of

postoperative infarction. In patients without aortic cross-clamping, a dry operative field was obtained either by snares or bulldog clamps proximal and distal to the site of coronary anastomosis. This procedure may lead to localized trauma to the coronary arteries, with resultant infarction. The status of the coronary bypass graft is likely to be of critical importance in the development of postoperative infarction in the presence of damage to the native coronary circulation.

Value of serum enzyme determinations: Dixon et al.[6] have stressed the need for creatine phosphokinase isoenzyme determinations in the assessment of postoperative infarction, since serum creatine phosphokinase and glutamic oxaloacetic transaminase levels are elevated by musculoskeletal operative trauma. However, several reports have noted good correlation between postoperative electrocardiographic changes and serum glutamic oxaloacetic transaminase and creatine phosphokinase levels in patients undergoing the Vineberg procedure.[1–4] In our series, serum glutamic oxaloacetic transaminase and creatine phosphokinase values of more than 200 and 2,000 units, respectively, separated patients with infarction from those without infarction. Only one patient with infarction did not show this enzyme pattern, and there were three false positive values.

Prognosis: Brewer et al.[5] noted that patients with infarction did not have a more severe postoperative course after bypass grafting than those without infarction. In our series, the two postoperative deaths occurred in patients with postoperative infarction. Both the shock syndrome and cardiac arrest noted in these patients may have been directly related to myocardial necrosis after operation. Thus, postoperative infarction may result in any of the usual complications of infarction including reduced cardiac output and arrhythmia.

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New Q Waves After Coronary Artery Bypass Surgery for Angina Pectoris

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Pre- and postoperative electrocardiograms were evaluated in 44 patients with angina pectoris who underwent single or multiple coronary artery bypass procedures. Two groups were identified: Group A, 37 patients with bypass procedures only, and Group B, 7 patients with bypass procedures and additional surgery (valve replacement in 4 and ventricular resection in 3).

Preoperative electrocardiograms showed abnormal Q waves in 14 of 37 patients in Group A and in 3 of 7 patients in Group B. After coronary artery bypass, new Q waves appeared in 11 of 37 patients (30 percent) in Group A, including 1 of 9 (11 percent) with one-vessel disease on preoperative coronary arteriograms, 7 of 20 (35 percent) with two-vessel disease and 3 of 8 (37.5 percent) with three-vessel disease; new intraventricular conduction abnormalities appeared in 4 of the 37. None of the seven patients in Group B had new Q waves postoperatively, but three had intraventricular conduction abnormalities. There was no correlation between new Q waves and preoperative values for left ventricular end-diastolic pressure. In Group A, new Q waves were demonstrated in 2 of 9 patients (22 percent) with one coronary bypass procedure, 5 of 21 patients (24 percent) with two bypass procedures and 4 of 6 patients (67 percent) with three bypass procedures. The single patient who had four coronary artery bypass procedures had no new Q waves after operation.

It is evident that the prevalence of new Q waves was greater in patients who had two- or three-vessel disease by coronary arteriography as well as in those who had three coronary artery bypasses. Postoperative clinical course and mortality were not affected.

Myocardial revascularization utilizing direct saphenous vein bypass graft has been used extensively, and several reports of postoperative electrocardiographic changes have appeared. Diethrich et al.[1] in 1968 reported electrocardiographic changes compatible with acute myocardial infarction in 11 of 40 patients (27.5 percent) who underwent the Vineberg procedure. The reported frequency of electrocardiographic changes compatible with myocardial infarction after coronary artery bypass has ranged from approximately 8 to 35 percent.[2–10] This electrocardiographic study was undertaken to assess the frequency of new Q waves after saphenous vein bypass surgery for occlusive coronary artery disease.

Material and Methods

The pre- and postoperative electrocardiograms, together with preoperative coronary arteriograms and left ventriculograms, were studied in 44 patients who underwent coronary artery bypass surgery at this hospital. Five other patients who died on the day of operation were not included because postoperative 12 lead electrocardiograms were not obtained. The study group comprised 37 men and 7 women whose ages ranged from 32 to 68 years.

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TABLE I

Analysis of Preoperative Electrocardiograms in 44 Cases

Previous myocardial infarction	17
Anterior	4
Inferior	12
Inferolateral	1
ST-T changes	20
Right bundle branch block	3*
Normal	5

* 1 had previous myocardial infarction.

TABLE II

Vessel Involvement by Coronary Arteriography

Vessels Involved (no.)	Cases (no.)	Previous Myocardial Infarction	New Q Waves	New Conduction Abnormalities	No Postoperative Change
Group A					
1	9	3	1(11%)	2	6
2	20	9	7(35%)	1	12
3	8	2	3(37%)	1	4
Total	37	14	11	4	22
Group B					
1	3	1	0	1	2
2	2	1	0	1	1
3	2	1	0	1	1
Total	7	3	0	3	4

TABLE III

Analysis of Postoperative Electrocardiograms in 44 Cases

	Group A		Group B	
	no.	%	no.	%
New Q waves	11	30	0	0
New conduction abnormalities	4	11	3	43
No change	22	59	4	57
Total	37	100	7	100

Since S–T segment and T wave changes occur frequently after cardiac surgery and their specificity for myocardial infarction is doubtful, only the QRS complexes were analyzed during this period. The New York Heart Association's criteria[11] for an abnormal Q wave were used. Pre- and postoperative abnormal Q waves were analyzed. Preoperative coronary arteriograms were obtained in all patients. Arterial obstruction of greater than 50 percent was considered significant, and the number of arteries involved was tabulated. Left ventricular end-diastolic pressure, determined in 38 patients, was considered abnormal if it exceeded 12 mm Hg. Postoperative electrocardiograms were analyzed by at least four of us, and new Q waves were correlated with selective coronary arteriographic data, left ventricular end-diastolic pressures and the number of arteries bypassed.

The 44 patients were classified in two groups. Group A comprised 37 patients who had single or multiple coronary artery bypass procedures only. Group B comprised seven patients who had single or multiple bypass procedures and additional surgery: valve replacement in four (two aortic and two mitral) and ventricular resection in three (for ventricular aneurysm [2 patients] and idiopathic hypertrophic subaortic stenosis [one patient]).

Results

Preoperative Findings

Preoperative electrocardiograms indicated previous myocardial infarction in 17 patients, 14 of 37 in Group A (38 percent) and 3 of 7 in Group B (43 percent). The infarction was located in the inferior wall in 12, the anterior wall in 4 and the inferolateral wall in 1. Right bundle branch block was present in three patients, including one with evidence of old myocardial infarction. Twenty patients had S–T segment and T wave changes only, and five had normal electrocardiographic findings (Table I).

Coronary arteriograms in Group A disclosed one-vessel disease in 9 patients, two-vessel disease in 20 and three-vessel disease in 8 (Table II). In Group B, one-vessel disease was present in three patients, two-vessel disease in two and three-vessel disease in two. Previous myocardial infarction was present in 4 of the 12 patients with one-vessel disease (3 in Group A and 1 in Group B), 10 of the 22 patients with two-vessel disease (9 in Group A and 1 in Group B) and 3 of the 10 patients with three-vessel disease (2 in Group A and 1 in Group B) (Table II).

Postoperative Findings

Postoperative electrocardiograms revealed abnormal new Q waves in 11 of the 37 patients in Group A (30 percent) but in none of the 7 patients in Group B. Four patients in Group A (11 percent) had new conduction abnormalities, intraventricular conduction delay (three patients) and left bundle branch block (one patient) (Table III). In Group B, three of seven patients (43 percent) manifested a new left bundle branch block.

Of the 11 patients in Group A who had new Q waves, only 2 (18 percent) had electrocardiographic evidence of previous myocardial infarction. Before operation, three of these patients had three-vessel disease, seven had two-vessel disease and one had one-vessel disease (Table II). Preoperative left ventricular end-diastolic pressure data were available in 32 patients in Group A and in 6 patients in Group B (Table IV). In Group A, 23 patients had normal values and 9 had increased values (13 to 33 mm Hg). In Group B, two patients had normal values and four had abnormal values (13 to 23 mm Hg). After coronary artery bypass, 6 patients in Group A with previously normal left ventricular end-diastolic pressure manifested new Q waves, 2 had conduction abnormalities and 15 showed no change; of the 9 patients with abnormal left ventricular end-diastolic pressure, 3 manifested new Q waves and 6 no change. In the two patients in Group B with normal left ventricular

end-diastolic pressure, one had a conduction abnormality and one showed no change. In the four patients with abnormal left ventricular end-diastolic pressure, two had conduction abnormalities only (Table IV).

In Group A, correlation of electrocardiographic data with the number of arteries bypassed (Table V) disclosed new Q waves in 2 of 9 patients (22 percent) who had one coronary artery bypass procedure, 5 of 21 patients (24 percent) who had two bypass procedures and 4 of 6 patients (67 percent) who had three bypass procedures. The single patient with four bypass grafts manifested no electrocardiographic changes after operation.

Of the 44 patients studied, 42 were discharged from the hospital and 2 died. The presence of new Q waves did not appear to affect hospital mortality rate. One patient with new Q waves postoperatively had mediastinitis and intraventricular conduction abnormality and died of sepsis. The other patient manifested a postoperative intraventricular conduction disturbance on the electrocardiogram and died with shock secondary to a bleeding disorder.

TABLE IV

Correlation of Left Ventricular End-Diastolic Pressure (LVEDP), Previous Myocardial Infarction and Electrocardiographic Changes

LVEDP	Patients (no.)	Previous Mycardial Infarction	New Q Waves	New Conduction Abnormalities	No Change
Group A					
Normal	23	8	6(26%)	2	15
Increased	9	4	3(33%)	0	6
Group B					
Normal	2	0	0	1	1
Increased	4	0	0	2	2

TABLE V

Pre- and Postoperative Electrocardiograms and Number of Coronary Bypasses

Bypass Grafts (no.)	Patients (no.)	New Q Waves	New Conduction Abnormalities	No Change
Group A				
1	9	2(22%)	0	7
2	21	5(23%)	4	12
3	6	4(66%)	0	2
4	1	0	0	1
Total	37	11	4	22
Group B				
1	3	0	1	2
2	2	0	1	1
3	2	0	1	1
4	0	0	0	0
Total	7	0	3	4

Discussion

The overall frequency of postoperative myocardial infarction in 12,712 patients who underwent a general surgical procedure during a 5 year period at the New York Hospital was reported to be 0.95 percent.[12] In the presence of previous postoperative myocardial infarction this rate rose to 6.5 percent. Our study reveals that of 37 patients who underwent coronary artery bypass surgery alone, 11 (29.7 percent) manifested new Q waves.

Transitory Q waves may be seen on the electrocardiogram under various circumstances and may not represent myocardial necrosis. Q waves were observed after shock and severe metabolic stress by Shugoll,[13] after cross-clamping of the aorta and during the initiation of extracorporeal circulation by Klein et al.[14] and during atrial pacing by De la Fuente et al.[15] The explanations given by these investigators do not apply to our study since the new Q waves in our patients were not transitory but persisted at least until discharge from the hospital. We believe that these Q waves represent acute myocardial infarction occurring during or immediately after coronary artery bypass surgery.

There have been attempts to evaluate objectively the accuracy of diagnosis of acute myocardial infarction after thoracic surgery. Although many factors may affect serum enzyme values, several reports suggest that these values correlate well with the presence or absence of myocardial infarction.[1,16–19] However, our patients did not have serial postoperative enzyme studies.

The frequency of postoperative myocardial infarction in patients undergoing a Vineberg procedure for coronary artery disease ranges from 9 to 27.5 percent.[1,16,17,20] The reported frequency of acute myocardial infarction after coronary artery bypass surgery has varied. Dawson et al.[2] reported a rate of 22 percent (30 of 134), Brewer et al.[3] a rate of 20 percent (49 of 243), Sheldon et al.[4] a rate of 9 percent (9 of 100) and Hultgren et al.[5] a rate of 34 percent (17 of 50); the latter series represents a mixed group of saphenous vein bypass grafts, Vineberg and other revascularization procedures. More recently, Anderson et al.[6] reported a 17 percent frequency (8 of 46), Kansal et al.[7] a 10 percent frequency (15 of 151) and Williams et al.[8] a 23 percent frequency (23 of 100). Vectorcardiographic analysis of acute myocardial infarction revealed a 6 percent prevalence (6 of 100) in the study of Friedewald et al.[9], an 8 percent prevalence (15 of 193) in that of Friedberg et al.[10] and a 35 percent prevalence (6 of 17) in that of Anderson et al.[6]

Selection of patients may be a significant factor in these differences since, in our patients with extensive disease requiring more than one bypass, acute myocardial infarction occurred more frequently than in those with less severe disease. The time that patients remained under extracorporeal circulation during operation was implicated by Brewer et al.,[3] who found that myocardial infarction occurred more frequently

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in patients who had more than 120 minutes of pump time.

The anoxic arrest of 10 to 15 minutes for each coronary artery anastomosed may be a significant factor in a patient with severe preexisting coronary artery disease. This was manifested in our study by a greater prevalence of new Q waves in patients with three coronary artery bypasses (67 percent) than in those with one or two bypasses (22 and 24 percent, respectively). Technical factors may also play a role in the development of myocardial infarction and should be evaluated and analyzed further. Recently a high rate of myocardial infarction after combined coronary endarterectomy and coronary artery bypass was reported,[2,21] but only one patient in our series had this procedure.

Nine of our patients who had no previous electrocardiographic evidence of myocardial infarction manifested new Q waves. However, of 14 patients with electrocardiographic changes of previous myocardial infarction, only 2 had new Q waves. New intraventricular conduction abnormalities that developed in four patients in Group A made the diagnosis of acute myocardial infarction impossible. Therefore, this change may have masked a higher frequency of new Q waves. None of the seven patients in Group B had new Q waves; however, four had new conduction abnormalities that may have masked the electrocardiographic findings. Electrocardiographic changes did not correlate significantly with preoperative left ventricular end-diastolic pressure data.

In conclusion, it appears that the greater the severity of coronary artery disease, the greater the prevalence of myocardial infarction after saphenous vein bypass surgery. The immediate operative mortality in our series was not affected. These electrocardiographic changes require further evaluation by longer follow-up studies, and their ultimate clinical significance should be considered in the overall evaluation of coronary artery bypass surgery.

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Correlation of Serum Magnesium Levels and Cardiac Digitalis Intoxication

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A prospective study was undertaken to compare the prevalence of hypomagnesemia and hypermagnesemia in patients with cardiac digitalis toxicity and in digitalized patients without toxicity. During an 8 month period on a general medical service, there were 38 patients with "definite" or "possible" digitalis toxicity, by serial electrocardiographic studies, among 120 digitalized patients whose serum magnesium levels were obtained. Serum magnesium concentrations were measured by atomic absorption spectrometry.

Hypomagnesemia was present in 21 percent of patients with and 10 percent of those without digitalis toxicity. Hypomagnesemia was not more prevalent in patients with toxicity but relatively lower serum levels of digoxin or digitoxin. The presence of hypermagnesemia was significantly greater in patients with toxicity (18 percent) than in those without toxicity (5 percent), and appeared to be related to a significantly greater prevalence of abnormal renal function in the former group. The potential value of magnesium administration in hypomagnesemic patients with cardiac digitalis toxicity warrants investigation. Caution should be exercised in the administration of magnesium sulfate to digitalis-toxic, azotemic patients who may already be hypermagnesemic.

It has been suggested that hypomagnesemia may contribute to the development of digitalis intoxication.[1–4] Animals made chronically magnesium deficient by diet[5–7] or rendered acutely hypomagnesemic by hemodialysis with a magnesium-free dialysate[3] show an increased sensitivity to digitalis with a lower threshold for toxic rhythm disturbances. A significant decrease in serum magnesium concentration has been reported in patients with congestive heart failure, and has been attributed to an increase in urinary magnesium excretion induced by diuretic agents.[8–11] Hypomagnesemia has been reported in patients with clinical digitalis intoxication,[3] and parenterally administered magnesium has suppressed rhythm disturbances caused by digitalis in both man and animals.[1,3]

The prospective study described here was undertaken to compare the prevalence of hypomagnesemia in patients having cardiac digitalis toxicity with that in digitalized patients without toxicity. Detailed epidemiologic data in these patients have been reported previously.[12]

Methods

All admissions to a single medical service were surveyed for an 8 month period. Drug histories were obtained on admission to determine whether a patient was taking a digitalis preparation up to at least 48 hours before entry. The prevalence of cardiac toxicity was determined by electrocardiographic criteria defined before the inception of the study. Patients manifesting ectopic ventricular arrhythmias, atrioventricular junctional escape or accelerated rhythms, paroxysmal atrial tachycardia with atrioventricular block, Mobitz type I second degree atrioventricular block or sinoatrial exit block were

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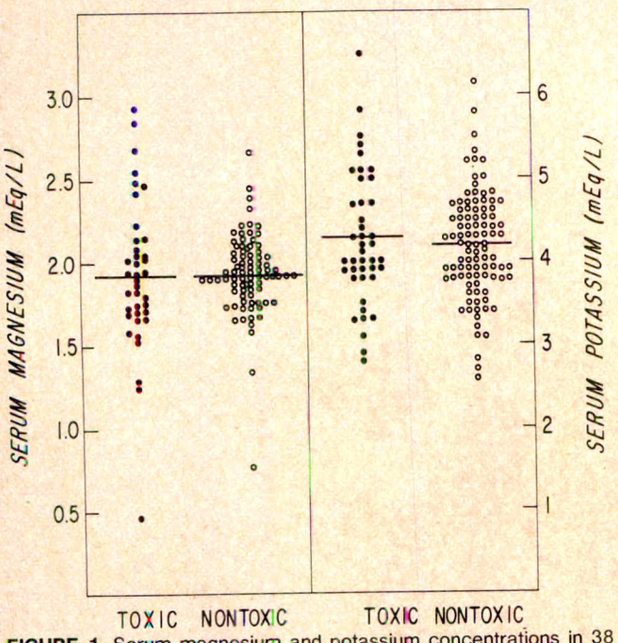

FIGURE 1. Serum magnesium and potassium concentrations in 38 patients with definite or possible digitalis toxicity and 82 patients without toxicity.

considered to have *definite* digitalis toxicity if the rhythm disturbance disappeared with discontinuance or reduction in dose of digitalis. Patients were considered to have *possible* toxicity if the aforementioned rhythm disturbances were only partially resolved with discontinuation of the drug or were associated with concomitant changes of acute myocardial infarction or ischemia, or if the patient left the hospital before complete serial electrocardiographic tracings could be obtained.

During the 8 month period of surveillance, 34 patients fulfilled the criteria for definite digitalis toxicity, and 9 patients were judged to have possible toxicity. During this period, 96 digitalized patients were admitted with no evidence of cardiac toxicity. Serum magnesium concentrations were measured by atomic absorption spectrometry[13,14] in 30 patients with definite and 8 with possible toxicity and 82 patients without toxicity admitted to the study; these patients represented 88 percent of the entire group. The accuracy of the serum magnesium measurements was determined by performing the analysis with use of both emission flame and atomic absorption spectroscopic techniques. Measurements of the same sera by the two methods gave virtually identical results using National Bureau of Standards certified standards.[13] The serum magnesium values were made known to the clinical investigators only after completion of the initial epidemiologic study[12] and were then correlated with clinical and biochemical data obtained from these patients. Serum magnesium determinations were performed in 16 healthy male volunteers, and the mean concentration in this group was 1.96 ± 0.26 (±2 standard deviations) mEq/liter. This range is comparable to normal values previously reported from this laboratory.[13,15,16] Hypomagnesemia was therefore defined as a serum magnesium level lower than 1.70 mEq/liter, which is 2 standard deviations below the mean for the control group.

Data pertaining to the type and dose of digitalis, supplementary medications such as diuretic agents, and clinical diagnoses were collected from patients with and without toxicity on admission to the study.

Blood urea nitrogen, serum creatinine, sodium (Na^+), potassium (K^+), chloride, bicarbonate and calcium were determined by standard laboratory techniques.

Duplicate determinations of serum digoxin and digitoxin concentrations were performed in the digitalized patients by radioimmunoassay methods previously reported.[17–19] Sera drawn from patients taking digitalis leaf were assayed for digitoxin concentration.

The means or prevalence percentages of all data were compared by Student's t test or the chi square test, where appropriate.

Results

Hypomagnesemia: Serum magnesium and potassium concentrations in the 30 definitely toxic, 8 possibly toxic and 82 nontoxic patients in whom these measurements were made are shown in Figure 1. Mean (± standard deviation) serum magnesium concentration was 1.93 ± 0.47 mEq/liter in patients with clinical toxicity (definite and possible) and 1.92 ± 0.24 in patients without toxicity. Thus, there was no significant difference between the two groups in mean serum magnesium or serum potassium values. However, the prevalence of patients with hypomagnesemia was two-fold greater in the group with digitalis toxicity ($0.05 < P < 0.10$). Hypomagnesemia (serum magnesium less than 1.70 mEq/liter) was found in 8 of 38 patients with definite or possible toxicity (21 percent) and in 8 of 82 patients without toxicity (10 percent). Hypokalemia, defined as a serum potassium value less than 3.5 mEq/liter, was present in 6 of the 38 patients with toxicity (16 percent) and in 11 of the 82 without toxicity (14 percent) (not significant). However, the combination of hypokalemia and hypomagnesemia was present in only one patient with toxicity and in no patient without toxicity.

There was no significant difference between use of diuretic agents in hypomagnesemic patients (56 percent) and in patients with normal or elevated serum magnesium levels (52 percent). Nineteen percent of digitalized hypomagnesemic patients were judged to be alcoholic, compared to a 7 percent prevalence of alcoholism in patients with normal or elevated serum magnesium levels (not significant). Twenty-five percent of hypomagnesemic patients and 28 percent of those with elevated or normal magnesium levels were diabetic. No patient had diabetic ketoacidosis when blood was drawn for serum magnesium determination. Only one patient in either group had clinical and laboratory evidence of intestinal malabsorption, and this patient had no digitalis toxicity and a normal serum magnesium concentration. Thus, there was no significant difference in the prevalence of diuretic administration, acute or chronic alcoholism, diabetes mellitus or malabsorption syndrome between hypomagnesemic patients and patients with normal or elevated serum magnesium levels.

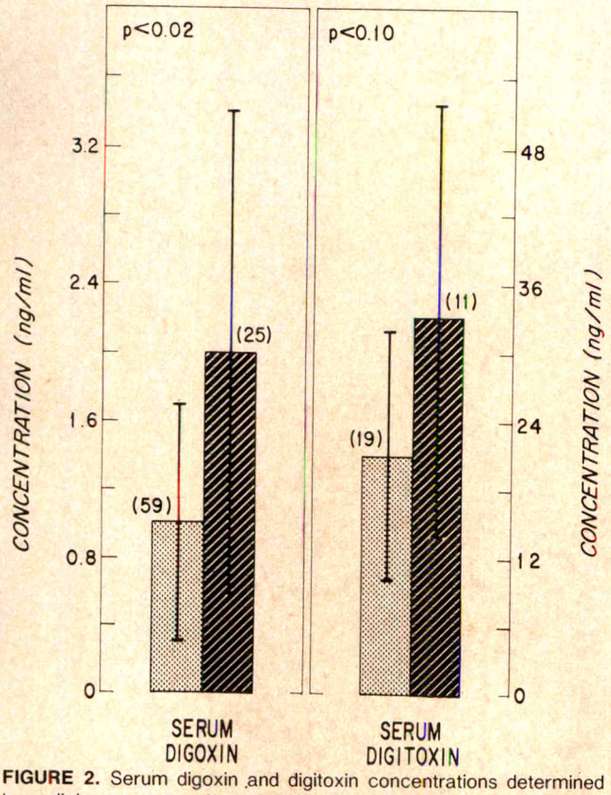

FIGURE 2. Serum digoxin and digitoxin concentrations determined by radioimmunoassay in patients without digitalis toxicity **(stippled bars)** and in patients with definite or possible digitalis toxicity **(hatched bars).** Data are presented as means ± standard deviation. The number of patients in each group is shown in parentheses.

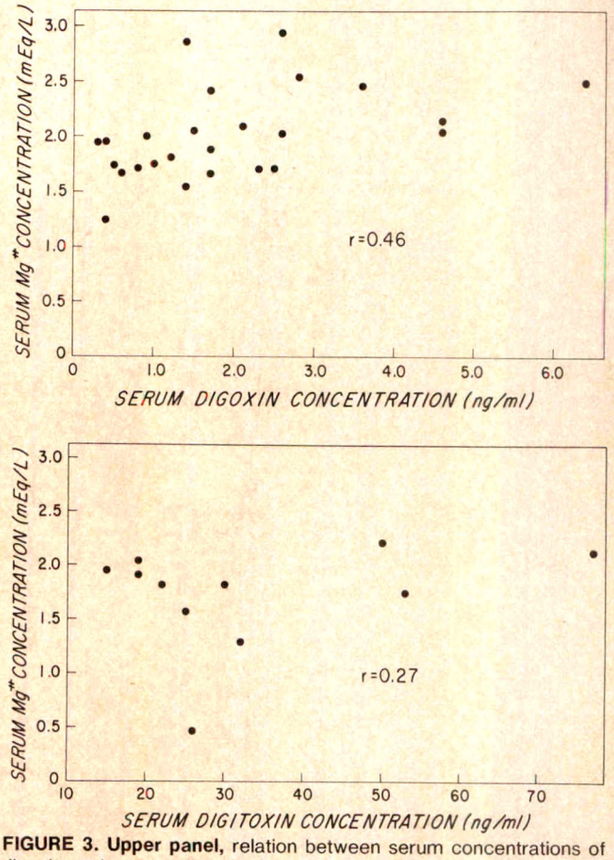

FIGURE 3. Upper panel, relation between serum concentrations of digoxin and magnesium in 25 patients receiving digoxin and manifesting toxicity. **Lower panel,** relation between serum digitoxin and magnesium concentrations in 11 patients receiving digitoxin or digitalis leaf and manifesting toxicity.

There was no significant difference between patients with and without toxicity in mean serum sodium, chloride, bicarbonate, and calcium concentrations.

Hypermagnesemia: The percentage of patients with hypermagnesemia was significantly higher in the group with toxicity than in the group without toxicity. Seven of 38 in the former group (18 percent) and 4 of 82 in the latter group (5 percent) had serum magnesium values greater than 2.22 mEq/liter. The mean (± standard deviation) serum creatinine and blood urea nitrogen concentrations were significantly higher in digitalized hypermagnesemic patients (creatinine 2.8 ± 1.9, blood urea nitrogen 65 ± 32 mg/100 ml) than in patients with normal or low serum magnesium levels (creatinine 1.3 ± 0.5, blood urea nitrogen 29 ± 16 mg/100 ml) (P <0.001). Hypermagnesemia has previously been reported in patients with azotemia.[20,21]

Serum digoxin and digitoxin levels: Mean serum digoxin and digitoxin concentrations in patients with and without toxicity who had serum magnesium levels determined in the study are shown in Figure 2. The mean serum digoxin concentration in the group with toxicity was 2.0 ± 1.5 (standard deviation) ng/ml compared to 1.0 ± 0.7 ng/ml in the group without toxicity (P <0.02). The mean serum digitoxin or digitalis leaf assayed as digitoxin in the group with toxicity was 33 ± 19 ng/ml compared to 21 ± 11 ng/ml in the group without toxicity ($0.05 < P < 0.10$). As shown by the standard deviations, there was considerable overlap in serum digitalis levels in the two groups.

The relation between serum digoxin and digitoxin levels and serum magnesium concentrations is shown in Figure 3. In the patients with toxicity, hypomagnesemia was not more prevalent among those with relatively lower levels of serum digoxin or digitoxin than in those with relatively higher levels. Three of 16 patients (19 percent) with serum digoxin levels less than 1.7 ng/ml or digitoxin levels less than 25 ng/ml were hypomagnesemic, whereas 4 of 20 (20 percent) patients with toxicity and serum digitalis levels greater than these values were hypomagnesemic. Thus, hypomagnesemia was not more prevalent, and did not appear to explain the increased sensitivity to digitalis in this group of patients with relatively lower serum concentrations of digoxin or digitoxin.

Discussion

Recent advances in the analytic methods for serum magnesium determination have made the rapid and accurate measurement of this ion a useful clinical tool in a variety of disease states. Our prospective study demonstrated a wide prevalence of hypomagnesemia in cardiac patients receiving digitalis glycosides. Hypomagnesemia occurred more frequently in patients with cardiac digitalis toxicity and was not associated with hypokalemia, although these findings were of borderline statistical significance. However, total body potassium may have been diminished in these patients without being reflected in the serum concentration. Hypermagnesemia was also more prevalent in patients with digitalis toxicity and was apparently related to the greater prevalence of impaired renal function in this group.

Causes for the development of hypomagnesemia: The causative factors for the low magnesium levels in the digitalized patients in our study are not apparent. Magnesium depletion has been reported to occur frequently in patients receiving diuretic agents,[8–11] and in patients with alcoholism,[22] diabetes mellitus[23] and intestinal malabsorption.[24] There was no increased prevalence of diuretic administration, alcoholism, diabetes mellitus or malabsorption in the group with hypomagnesemia. However, other possible etiologic factors such as nutritional status were not investigated in detail.

Magnesium and digitalis toxicity: Increased sensitivity to the development of toxic rhythm disturbances has been observed when digitalis has been administered to monkeys[5] and puppies[6] made magnesium-deficient by dietary means. Less glycoside was required to produce cardiac arrhythmias, and the duration of the arrhythmia was significantly longer than in control animals.[7] In another study, serial acetyl strophanthidin infusions in dogs made hypomagnesemic by Kiil kidney dialysis with a magnesium-free dialysate demonstrated a 26 percent reduction in the amount of acetyl strophanthidin required to produce a toxic arrhythmia.[3] Intravenous infusion of magnesium sulfate subsequently suppressed the arrhythmias in the majority of these animals. Cats intentionally made digitalis-toxic to the point where ventricular ectopic beats developed responded with restoration of sinus rhythm when magnesium sulfate was administered.[1] Empirically, parenterally administered magnesium has also been found effective in abolishing ventricular bigeminy and ventricular tachycardia in patients with cardiac digitalis-toxicity.[1] In addition, magnesium depletion has been shown to alter the myocardial uptake of tritiated digoxin; more of the drug was found in myocardial tissue of magnesium-deficient animals more than 3 hours after administration.[25]

Clinical implication: Our study showed a rather wide prevalence of hypomagnesemia in digitalized cardiac patients. Investigation of the efficacy of magnesium administration in hypomagnesemic patients with cardiac digitalis toxicity seems warranted. Caution should be used in the parenteral administration of magnesium sulfate to azotemic patients who may already be hypermagnesemic. Routine measurement of the serum magnesium concentrations in digitalized patients, or those taking diuretic agents, may obviate this problem.

Acknowledgment

The excellent technical assistance of Mrs. Kirsten Johansen is gratefully acknowledged. We also thank Miss Ella Munro for her assistance in the statistical analyses.

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Influence of Exercise on Arrhythmias Induced by Digitalis-Diuretic Therapy in Patients with Atrial Fibrillation

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Serial low-level treadmill exercise testing was performed by 20 ambulatory patients with atrial fibrillation to provoke and study drug-related arrhythmias. All 20 were receiving long-term digitalis therapy; 19 were also receiving potassium-losing diuretic agents, and 3 had hypokalemia. The subjects were selected on the basis of resting electrocardiograms compatible with strong digitalis effects: prominent ST–T–U changes, intermittently occurring junctional beats, controlled ventricular rates (range 40 to 70/min) or ventricular premature beats. Arrhythmias suggesting digitoxicity were induced by exercise in all 20 subjects. Those occurring most often were junctional tachycardia with or without Wenckebach exit block, frequent ventricular premature beats and bigeminy. Idioventricular rhythm was induced in two subjects and ventricular parasystole in one. After withdrawal of digitalis and diuretic agents, subsequent exercise tests demonstrated increased ventricular rates, a decrease in ST–T–U changes and in the occurrence of most arrhythmias. In 18 patients, brief runs of junctional tachycardia persisted but occurred less often. Low-level exercise testing provides a simple method for provoking latent cardiac irritability in patients with suspected digitalis and diuretic toxicity; serial exercise testing after withdrawal of the drugs can demonstrate the devolution of arrhythmias.

Although digitalis remains the most important drug for treating heart disease, the appropriate dose is not always easily determined for individual patients. The problem of prescribing digitalis is often complicated by the concomitant use of potent electrolyte-deranging diuretic agents. In these circumstances, even small or otherwise appropriate doses of digitalis may produce unwanted arrhythmias or other toxic changes. Whether to increase, decreass or stop digitalis-diuretic administration often poses a clinical dilemma. The ventricular rate response to exercise has been extensively studied and provides a well known guide to digitalis therapy in patients with atrial fibrillation.[1–6] Although exercise is known to provoke rhythm and conduction disturbances,[7–10] there has been no systematic study of exercise-induced arrhythmias in relation to digitalis therapy. This report describes the use of low-level treadmill electrocardiographic tests to assess sequential exercise-induced arrhythmic changes before and after withdrawal of both digitalis and diuretic agents.

Subjects and Methods

The 20 subjects of this study were ambulatory patients with heart disease who had been referred for evaluation. They had been receiving long-term maintenance doses of a digitalis preparation (digoxin in 19 patients, digitoxin in 1 patient). Nineteen patients had also been taking potassium-losing diuretic agents without potassium supplements for several months. Nineteen had rheumatic heart disease, and one had coronary artery disease. One patient had mild nausea and anorexia, and others were asymptomatic. Hypo-

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kalemia (serum potassium less than 3.5 mEq/liter) was present in three patients. None had renal insufficiency, as judged by blood urea nitrogen concentrations. All patients had atrial fibrillation and were selected for serial exercise testing on the basis of 12-lead electrocardiographic findings suggesting a strong digitalis effect or digitalis excess. The electrocardiographic changes included slow ventricular rates (40 to 70/min), prominent ST–T–U wave changes, occasionally regular R–R intervals (all subjects) or the presence of junctional or ventricular premature beats. One patient had bigeminy, and 12 patients had brief runs of junctional tachycardia in the 2 minutes immediately before exercise.

Each patient walked on a 7 percent grade motorized treadmill with increasing increments in speed at 3 minute intervals. Bipolar electrocardiographic lead V_5 or V_6 was recorded continuously before, during and for 8 minutes after exercise. Exercise was limited to low levels: usually to a peak level of 1 or 2 miles/hour; an occasional patient walked comfortably at 3 miles/hour. The duration of exercise was often brief (range 1 minute, 10 seconds to 8 minutes, 5 seconds). Exercise was stopped with the appearance of mild dyspnea or fatigue, or both. After the first exercise test, digitalis and diuretic agents were discontinued and orally administered potassium chloride was prescribed. Similar exercise tests were repeated periodically over several days to assess sequential changes in cardiac rhythm and rate. Digitalis therapy was reinstituted and exercise testing discontinued if signs of cardiac congestion appeared or resting ventricular rates became persistently rapid. Each patient underwent more than one exercise test (Table I), the number depending on patient availability and time of disappearance of electrocardiographic signs of digitalis excess. The 20 patients performed a total of 72 exercise tests. The interval between the first and last exercise tests ranged from 5 to 27 days (mean 9.4).

TABLE I

Distribution of 72 Exercise Tests in 20 Subjects

Subjects (no.)	Exercise Tests: no. per Subject	Exercise Tests: Total no.
3	2	6
8	3	24
5	4	20
2	5	10
2	6	12
20		72

TABLE II

Arrhythmias Induced by Exercise Testing

Arrhythmia	During or Immediately After Exercise: no. of Subjects First Test	Trends on Serial Testing	
Junctional	20	Less frequent	18
		Disappeared	2
Junctional tachycardia with Wenckebach exit block	13	Disappeared	3
		Persisted	10
		New appearance	7
Wide QRS beats (ventricular ectopic beats or aberrant beats)	20	Disappeared	1
		Less frequent	16
		More frequent	3
Bigeminy	11	Disappeared	10
		Persisted	1
Idioventricular rhythm	2	Disappeared	2
Ventricular parasystole	1	Disappeared	1

Definition of Terms

Junctional beats in the presence of atrial fibrillation were identified by the occurrence of several pairs with identical R–R intervals and similar QRS configuration.[11,12] The second beat of each such pair was presumed to be of junctional origin whether formed by automatic activity or by intranodal reciprocal mechanisms. Junctional rhythms were recognized by "regularization of ventricular response" [13–16] with at least five successive beats of similar R–R intervals (within 0.02 second).[16–18] If the manifest rates exceeded 60/min, the term *junctional tachycardia* was used.[12,16] We did not differentiate the paroxysmal from the nonparoxysmal type although appearance of the latter has been considered an indication for discontinuing digitalis therapy.[19,20] The main reason for not using this well known classification is the appearance of many bouts of junctional tachycardia, often with widely differing rates, during a single exercise test. Difficulties with this classification have also been recognized by others.[17]

Junctional tachycardia with Wenckebach exit block was identified by grouping of beats exhibiting a progressive decrement in R–R intervals followed by a pause of less than twice the length of the preceding R–R interval. The R–R interval preceding the pause, by definition, was the shortest interval of the sequence. In addition, we required the presence of at least three such successive groupings to avoid a false diagnosis of Wenckebach exit block due to a chance occurrence of such beats in atrial fibrillation. The cycle length of the basic junctional focus was derived by dividing the duration of an individual Wenckebach grouping by the number of observed QRS complexes plus one[16,21–23] (Fig. 1). Second degree exit block of the 2:1, 3:1 or 4:1 type was recognized by the presence of frequent R–R intervals that were exact multiples of the cycle lengths of observed junctional tachycardia, as calculated from the Wenckebach sequences.[16,21] In many instances, junctional beats and junctional tachycardia might be thought to result from reciprocal mechanisms, but the absence of P waves rendered this degree of definition uncertain.[16,24,25]

Wide QRS complexes (0.10 second or more) may be designated as ventricular premature beats or aberrantly conducted supraventricular beats with the aid of the criteria suggested by Marriott and Sandler.[26] This classification is not entirely adequate,[27] and lead V_1 was not used in this study. However, the presence of aberration was suggested, although not proved, when wide QRS beats occurred at times when a supraventricular beat was expected in groups of beats interpreted as junctional tachycardia with Wenckebach exit block (Fig. 1). Runs of bigeminy due to aberrancy and those due to ventricular ectopy were not differentiated since we were unable to obtain His bundle recordings during walking exercise.

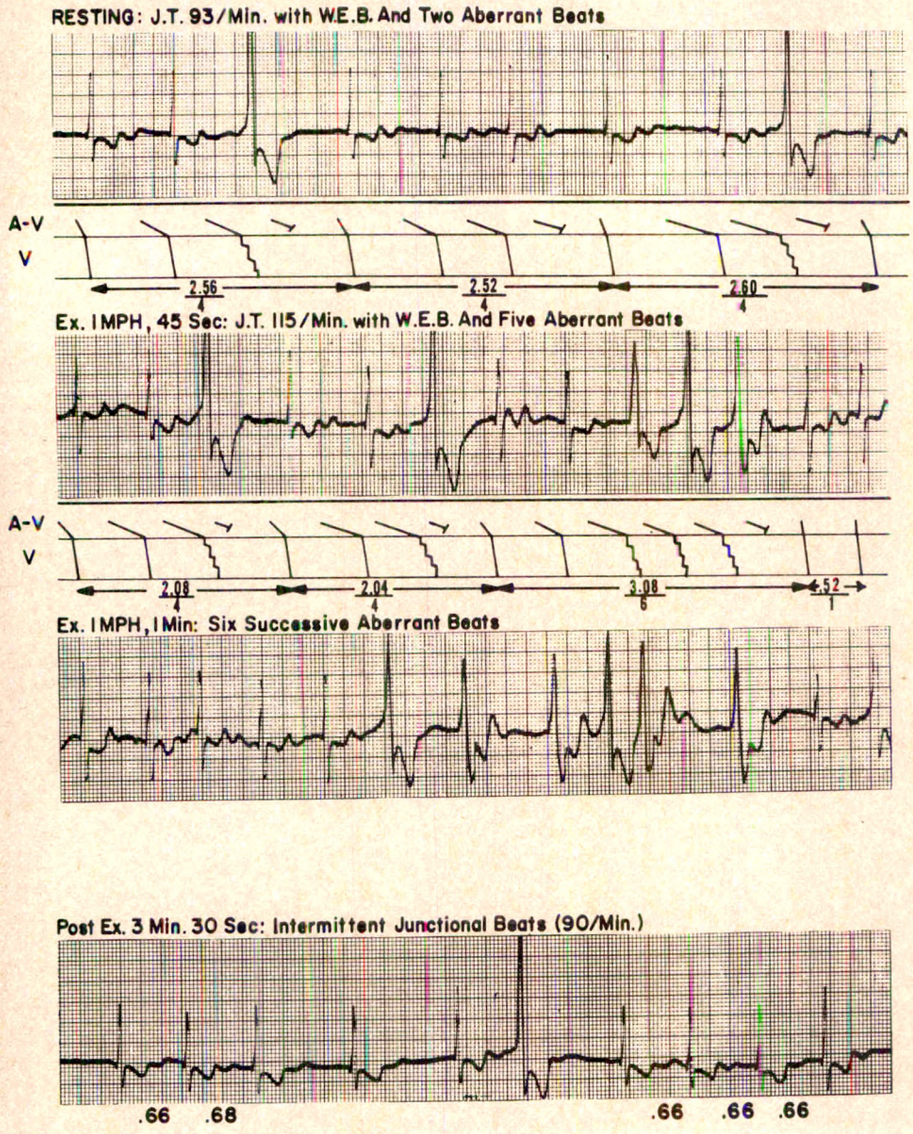

FIGURE 1. Selected portions of the first exercise electrocardiogram of a patient with rheumatic heart disease, before discontinuation of digoxin and furosemide. Junctional rhythm is present at rest in addition to two wide QRS complexes. With walking at 1 mile/hour **(second strip),** wide QRS beats occur more frequently; their appearance in Wenckebach groupings along with other beats with narrow QRS configuration in similar sequences suggests that they may be due to aberrancy. Later **(third strip)** beats of identical configuration appear without a Wenckebach grouping. Both wide QRS beats and junctional mechanisms were absent during the fourth exercise test, 6 days later. J.T. = junctional tachycardia; W.E.B. = with exit block.

Results

The first exercise test increased arrhythmias in all patients (Table II). With serial testing, exercise-induced ST–T–U changes became less prominent; ventricular rates gradually became more rapid, and the arrhythmias attributed to digitalis-diuretic excess tended to diminish or disappear. After each patient was studied, administration of digoxin was resumed, usually at similar dose schedules but without concomitant daily use of potent diuretic agents.

Junctional rhythms: Brief paroxysms of junctional rhythm with rates of 38 to 154/min were evident in 12 of the 20 patients' electrocardiograms recorded immediately before the first exercise test (Fig. 1 and 2). They were not found in the subsequent preexercise electrocardiograms of 9 of these 12 patients; 4 additional patients had junctional rhythm at rest for the first time in later tests only. Electrocardiograms recorded during and after exercise revealed junctional tachycardia, with rates between 71 and 210/min, in 70 recordings (97 percent) (Fig. 1 to 3). The first paroxysm of junctional tachycardia usually began within a few seconds after the beginning of exercise and the duration of each episode was usually limited to approximately 10 to 20 seconds. Long runs of junctional tachycardia, lasting 30 seconds or more, were encountered in only one patient. The rates of junctional rhythms varied from time to time during the same test, with a tendency toward acceleration during exercise (Fig. 1, 2 and 4). On serial testing, the rates of junctional rhythm became faster in eight patients, remained similar in six patients and varied inconsistently from test to test in six patients. The occurrence of junctional tachycardia tended to be less frequent in the later tests, although brief runs of this arrhythmia were evident in the last tests of 18 patients.

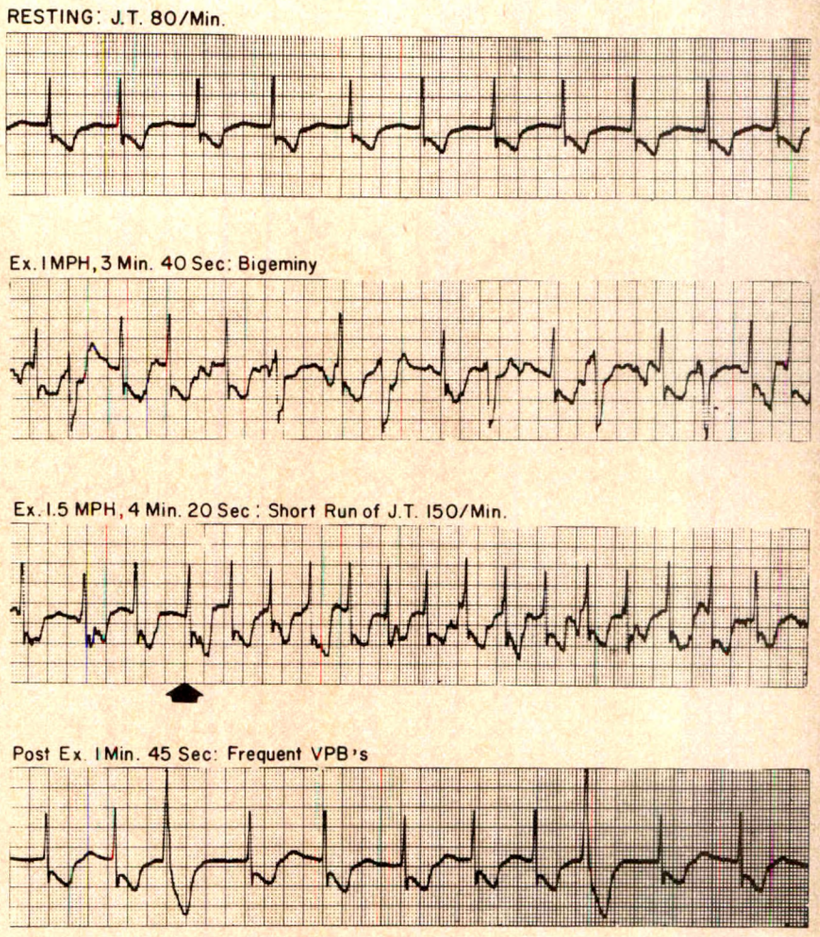

FIGURE 2. Exercise electrocardiogram of patient taking digoxin and a thiazide diuretic agent. The resting tracing showed intermittent runs of junctional rhythm. At 1 mile/hour bigeminal sequences are induced. At 1.5 miles/hour a short burst of junctional tachycardia (J.T.) is seen **(onset at arrow).** After exercise, ectopic beats are still present and the U waves are more prominent. VPB's = ventricular premature beats.

Junctional exit block: Four patients had intermittent junctional rhythm with Wenckebach periods on the preexercise electrocardiogram (Fig. 1); in 13 patients these changes developed during exercise. Wenckebach groupings continued to appear with exercise long after the drugs had been discontinued. When Wenckebach exit block occurred in more than one exercise test (four patients), it usually appeared with higher rates in the later tests.

Ventricular premature beats: Frequent ventricular premature beats were seen on the immediate preexercise electrocardiogram of 3 subjects and were induced in the first exercise test of 10 patients. With subsequent testing, they tended to appear less often in seven patients, disappeared in one patient and increased in two patients. With exercise, 13 of 20 patients had increased frequency of wide QRS beats that may have been either ventricular in origin or aberrant. These beats were often of multiform configuration and, when they occurred in succession, simulated ventricular tachycardia on casual inspection (Fig. 1). They were usually independent of preceding cycle lengths. On serial testing they appeared less frequently in 12 patients and tended to be of more uniform configuration. In one patient they appeared more frequently during the course of five serial tests. In one patient, ventricular parasystole developed during the first two tests but not in the three tests performed after the withdrawal of drugs. Two patients had runs of idioventricular rhythm during their first exercise test and none thereafter. Paired ventricular beats were seen occasionally, but runs of regular ventricular tachycardia were not encountered.

Bigeminy: Wide QRS bigeminy was seen intermittently in one patient before exercise. Bigeminy due either to ventricular premature beats or to aberrant beats was seen in an additional 10 patients on the first treadmill exercise electrocardiogram, both during and after exercise (Fig. 2, 5 and 6). Bigeminy failed to appear on serial testing in all but one patient in whom it appeared briefly in all six tests performed.

Discussion

Determination of digitalis dosage for the individual patient remains a clinical decision. The net result of digitalis action on each patient, influenced by many known and unknown factors, continues to provide clinical guidelines for digitalis requirements. The identification of digitoxicity has been the subject of many investigations. Attention has been drawn to the

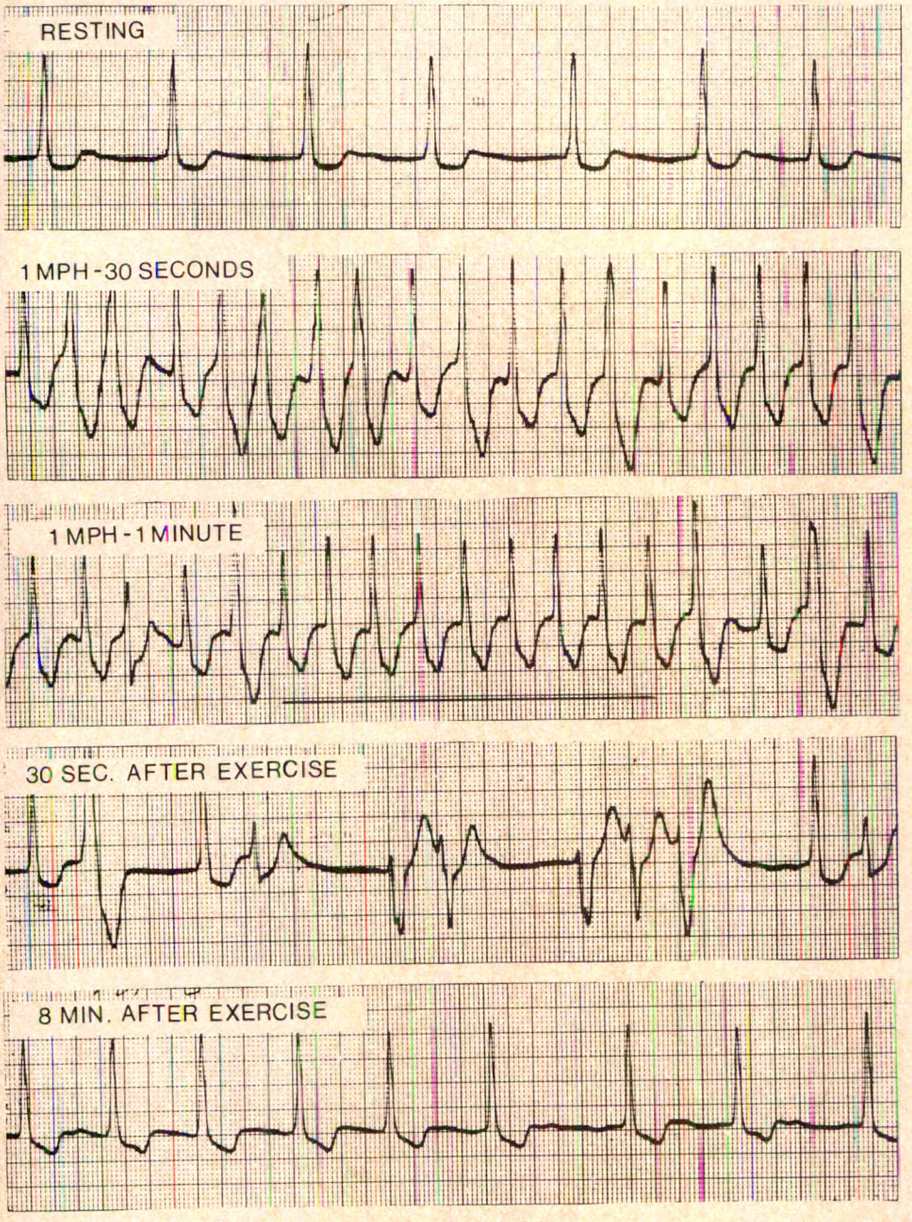

FIGURE 3. Portions of exercise electrocardiogram of a 52 year old man with rheumatic mitral regurgitation. He had been taking digoxin and daily doses of furosemide for many months. The resting record shows a slow (nearly regular) ventricular rate and ST–T–U changes. During walking at 1 mile/hour, the ST–T changes are more marked and the ventricular rate is rapid. After 1 minute of walking a brief run of junctional tachycardia is seen **(third strip)**. After exercise, the rate slows abruptly with pauses interrupted by several wide QRS escape beats. Eight minutes of rest was required to return the electrocardiographic pattern to the preexercise condition. Serial testing after discontinuation of the drugs revealed a gradual decline in these changes over a 16 day period.

pulse or heart rate at rest and after exercise, particularly in patients with atrial fibrillation, for evaluating the adequacy of digitalis therapy. Several digitalis-related arrhythmias occurring at rest have been recognized as having important prognostic implications. These include atrial tachycardia with various degrees of block, junctional rhythms, frequent ventricular beats and ventricular tachycardia. On the basis of an analysis of resting electrocardiograms, junctional tachycardia has been classified as paroxysmal or nonparoxysmal depending on heart rate[19]; and appearance of the nonparoxysmal type has been considered an indication for discontinuing administration of digitalis.[19,20,23] In our study, gross variations in the manifest rates of junctional tachycardia, both paroxysmal and nonparoxysmal forms, was observed in every patient during and after exercise. Classifying exercise-induced junctional tachycardia on this basis and assigning different etiologic, therapeutic and prognostic implications does not seem justified.

Recent methods for assaying blood glycoside levels have proved valuable in some cases, but the untoward effects of digitalis are not consistently reflected by such measurements.[28–30] Serum digoxin determinations were not available for the 20 subjects during the period of our study. However, in the subsequent evaluation of 14 additional patients with similar exercise-induced arrhythmias, we found only four (35 percent) with elevated digoxin levels in excess of 2.2 ng/ml.

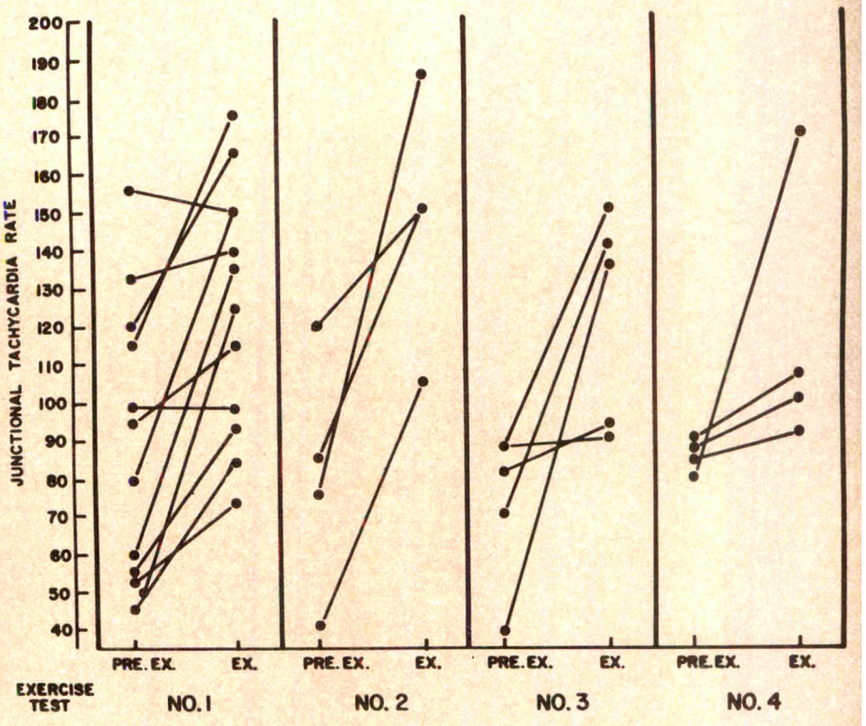

FIGURE 4. Heart rates during brief runs of junctional rhythm before (PRE. EX.) and during exercise (EX.) Digitalis and diuretic agents had been discontinued after the first test. With serial testing fewer patients had junctional rhythms and these arrhythmias occurred less frequently, persisting in four. Exercise produced faster rates with few exceptions.

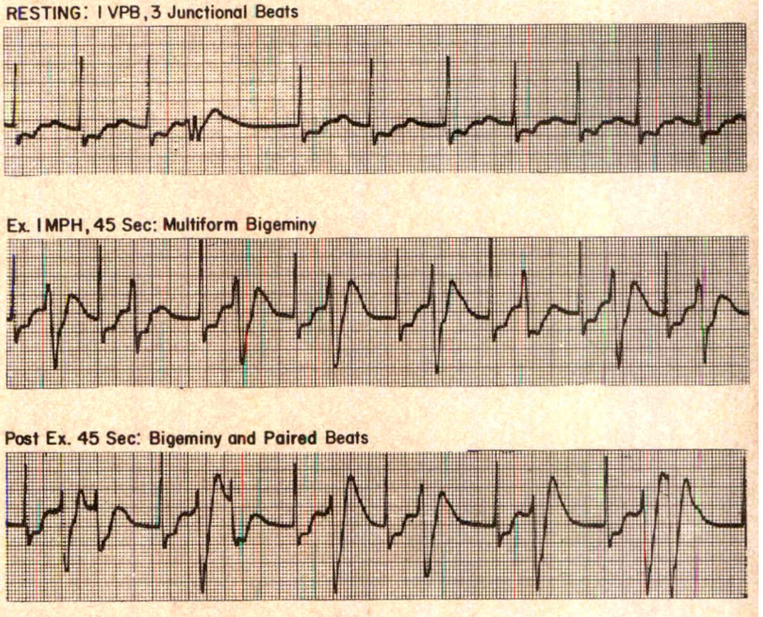

FIGURE 5. First exercise test of a 42 year old woman with chronic mitral valve disease. At rest, ST–T–U changes are present as well as some regular R–R intervals and an occasional wide QRS early beat. Walking at 1 mile/hour **(second strip)** induced bigeminy which persisted throughout exercise and for several minutes after exercise **(third strip).** Paired beats also occurred after exercise. VPB = ventricular premature beat.

A few brief and fragmentary references are available on the possible influence of exercise on digitalis-induced arrhythmias. Lown and Levine[15] noted that "slight exertion, deprivation of oxygen therapy, straining on the bed pan or emotional upset" may bring on bigeminy in digitoxic patients. Scherf and Cohen[17] suggested an accelerating effect of exercise on junctional tachycardia as a differential feature to distinguish this arrhythmia due to digitoxicity from the so-called paroxysmal type. Gooch and McConnell[9] recorded an instance of exercise-induced tachyarrhythmias that did not reappear on repeat exercise tests performed after the digitalis dose was decreased. Surawicz and Mortelmans[31] cite a patient with atrial fibrillation and a slow ventricular rate and bigeminy at rest who had a more rapid rate after walking. Examination of their tracing reveals intermittent junctional mechanisms accelerated by exercise. In reporting the "effect of different digoxin doses on subjective symptoms and physical working

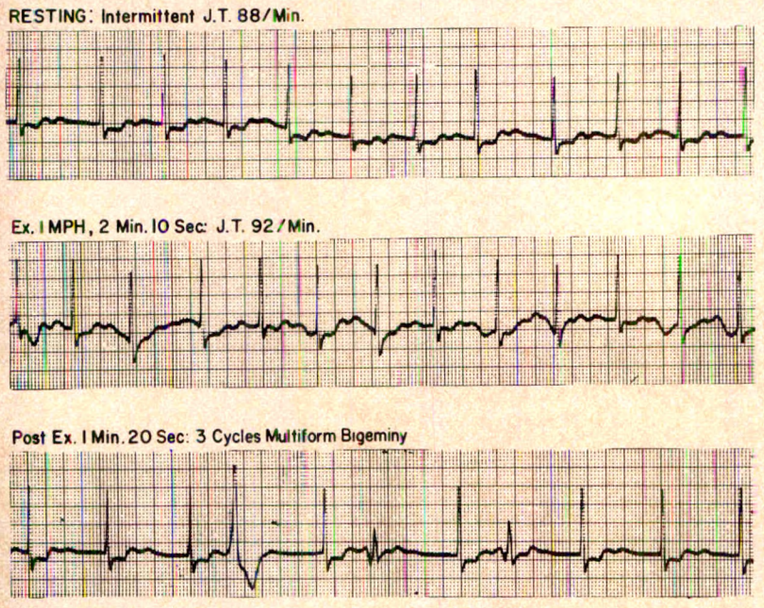

FIGURE 6. Second exercise test (same patient as in Fig. 5) performed 4 days after discontinuation of digoxin and diuretic therapy. Regular (junctional) intervals (J.T.) are still present at rest. Bigeminy continues to be present although it is less frequent, of multiform configuration, and occurs only after exercise.

capacity" and "digoxin dosage and ventricular rates at rest and exercise," Redfors[6] observed an increase in the number of aberrant beats during exercise in patients with atrial fibrillation receiving digoxin.

The persistence of brief paroxysms of junctional tachycardia in 90 percent and Wenckebach exit block in 65 percent of our patients after withdrawal of digitalis and diuretic agents deserves comment. Junctional tachycardia did not occur in long regular runs but in brief groupings, as recorded by Chung.[32] Apparently these arrhythmias with incomplete atrioventricular dissociation outlast the period of "digitoxicity" as reflected by both the response of ventricular rate to exercise and the appearance of cardiac decompensation requiring redigitalization. Perhaps they are due to more prolonged effects of electrolyte derangements on the heart although not indicated by serum potassium levels. Also, in some patients with atrial fibrillation, enhancement of junctional mechanisms may be a usual response to exercise rather than an indication of excessive digitalis.

In contrast to ventricular premature beats, aberrant beats are not usually considered a manifestation of digitalis excess.[33,34] Similarly, intraventricular conduction defects are not usually attributed to digitoxicity,[15,23,33] In our study, exercise frequently induced beats suggestive of aberrancy in several patients during their first test. These beats were not related to preceding cycle length or to rate-related changes of physiologic refractory periods. The gradual decrease of these beats in later tests in most patients suggests that their appearance had been provoked either by a direct action of the drugs on conducting tissue or by an overall effect of slower rates. The tendency toward multiform beats only in the earlier tests may also have a similar significance. Although this evidence is suggestive, further study is needed regarding the influence of digitalis on aberrant conduction.

Digitalis has been identified as one cause of bigeminy.[35–37] Bigeminy was apparent on the resting electrocardiogram of only one of our patients but appeared during exercise in 11. It disappeared in all but one in subsequent tests. The persistence of short runs of bigeminy in all six tests of one patient might be related to the underlying heart disease rather than to the effect of drugs.

It seems appropriate to compare the results of our study with the systematic observations by Redfors[6] concerning digitalis-induced arrhythmias during exercise. Junctional rhythms were not observed in his patients, although the sophisticated methods of his study were well adapted to identify such arrhythmias. He found aberrant beats to be more frequent during exercise in 65 percent (9 of 14) of the patients receiving digoxin, but the frequency of exercise-induced aberrancy increased with increasing doses of digoxin in only 14 percent (2 of 14) of patients. No difference was noted in the frequency of ventricular ectopic beats at rest and during exercise in the two patients who had such beats. Thus, with reference to junctional tachycardia and wide QRS beats, the findings of Redfors are at variance with ours. This discrepancy may be due to the prolonged use of electrolyte-deranging diuretic agents in our subjects and to the fact that our patients had had no abrupt changes in digitalis dosage for several months or years before the first exercise test.

Clinical implications: Junctional rhythm with or without exit block, ventricular ectopic beats and bigeminy are commonly seen with digitoxicity. The underlying metabolic and electrophysiologic mechanisms responsible for the increased arrhythmicity during and after exercise are beyond the scope of our clinical study. The tendency of arrhythmias to decrease or disappear after withdrawal of digitalis and diuretic agents suggests a decisive influence of drugs. The concurrent appearance and parallel behavior of

idioventricular rhythm and parasystole may indicate a similar relation. Nineteen of the patients of our study had no symptoms that could be specifically attributed to digitoxicity although all of them had chronic fatigue, as indicated by reported improvement during the study period. When first seen, only one patient had occasional nausea and loss of appetite. These symptoms cleared after discontinuation of digitalis and diuretic therapy.

A diagnosis of digitalis-related arrhythmias may be suspected but cannot be confirmed by performance of only one exercise test. The demonstration of arrhythmic change with exercise may be related to the underlying cardiac condition, and serial testing after withdrawal of drugs is needed to indicate cause-and-effect relations. For example, exercise may induce ventricular bigeminy, and subsequent testing over several weeks may demonstrate a persistence of the arrhythmia[38] long after the disappearance of any possible drug effect. Maximal exercise levels were not necessary to induce the arrhythmias in our study, and treadmill walking to high levels is not recommended in such patients.

The resting 12 lead electrocardiogram of all patients was indicative of strong digitalis-diuretic effect (or mild digitoxicity, depending on arbitrary definitions). In searching for patients with such changes for inclusion in our study, we found only one who was not also being treated with potassium-losing diuretic agents. Because electrolyte-deranging diuretic agents may enhance the effect of digitalis, with or without hypokalemia,[15,35] the transient exercise-induced arrhythmias were probably due to the combination of drugs.

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Effect of Procainamide on Fibrillation Threshold of Normal and Ischemic Ventricles

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The effect of procainamide on ventricular fibrillation threshold was studied in anesthetized open chest hearts in 12 dogs without coronary occlusion and in 11 dogs during acute coronary occlusion. The minimal current required to induce ventricular fibrillation was determined by delivering a train of rapid rectangular pulses (100/sec) to the ventricle during its vulnerable period. Procainamide was administered as a single intravenous injection in a dose of 10 to 20 mg/kg body weight. Blood levels of the drug reached their peak immediately, fell to therapeutic levels (5 to 10 μg/ml) within about 30 minutes and then remained at those levels up to 80 minutes after the injection. The effect of procainamide on the fibrillation threshold correlated with procainamide blood levels. The increase, peak level and decrease in blood concentration paralleled changes in fibrillation threshold. Procainamide at therapeutic blood levels increased the mean fibrillation threshold from the control value of 16 to 30 ma (88 percent increase) in the normal ventricles. The effect was less pronounced during acute coronary occlusion, and the mean fibrillation threshold increased from 8 to 13 ma (63 percent increase) at therapeutic procainamide blood levels. In addition, procainamide failed to produce complete reversion of the decreased fibrillation threshold to the normal value during acute myocardial ischemia.

The major cause of death in patients with acute myocardial infarction is ventricular fibrillation. Ventricular premature beats are the most common arrhythmia observed during acute myocardial infarction and are a precursor of ventricular fibrillation. Lidocaine and procainamide have been extensively used in the management of patients in the coronary care unit and have proved effective in suppressing ventricular premature beats and reducing the incidence of ventricular fibrillation. It has recently been shown[1] that lidocaine decreases ventricular vulnerability to fibrillation by increasing the threshold for fibrillation during acute myocardial ischemia. This study was undertaken to investigate the effect of procainamide on the fibrillation threshold of normal and ischemic dog ventricles.

Methods

Experiments were performed in mongrel dogs anesthetized by an intravenous injection of sodium pentobarbital (30 to 35 mg/kg). Under artificial respiration, the chest was opened at the midline, and the heart was cradled in the opened pericardium. The sinoatrial node was crushed to permit pacing the heart at a constant rate by applying electrical stimuli to the ventricle. For reversible occlusion of the anterior descending branch of the left coronary artery, the artery was dissected free for a few millimeters near its origin and a snare was applied around the vessel. Procainamide was administered through a cannulated femoral vein. A femoral artery was also cannulated to obtain arterial samples for determination of blood procainamide levels and blood gas, and to record arterial pressure. Arterial blood gas and pH were frequently

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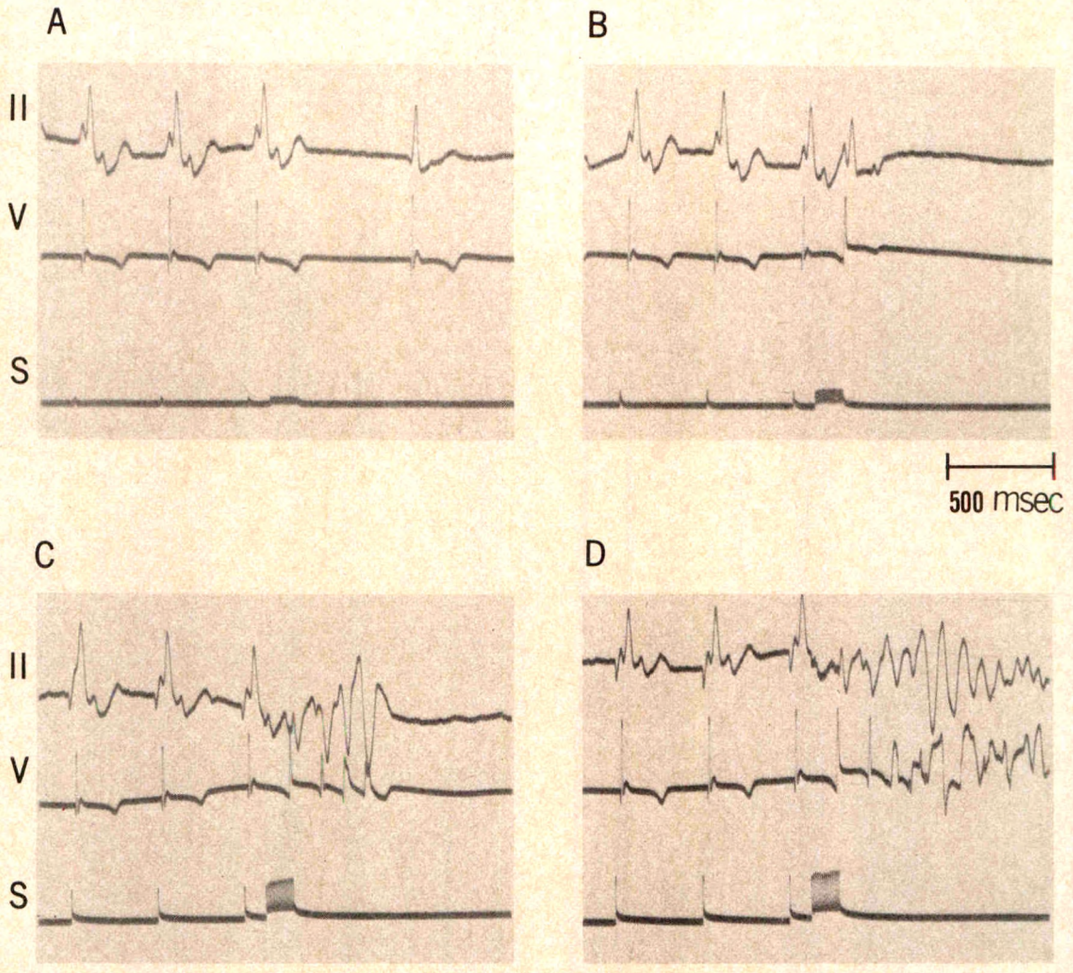

FIGURE 1. Determination of ventricular fibrillation threshold by applying the train of rapid rectangular pulses (100/sec) during the vulnerable period. II indicates lead II electrocardiogram; V, local electrogram recorded from a site close to the stimulating electrodes; and S, the artifact of stimuli applied through the bipolar stimulating electrodes attached to the anterior septal margin of the right ventricle. The intensity of the rapid pulses was gradually increased from **A** to **D.** A subthreshold intensity of the rapid stimuli produced no premature beat in **A.** Stronger rapid stimuli produced one premature beat in **B** and four premature beats in **C.** Further increase in the intensity of the stimuli resulted in fibrillation in **D.**

checked and were corrected when necessary to prevent respiratory or metabolic imbalance.

The bipolar stimulating and recording electrodes were small steel hooks with an interelectrode distance of 3 to 4 mm. The stimulating electrodes were attached to the anterior septal margin of the right ventricle about 10 mm from the edge of the area of expected ischemia. The recording electrodes were attached to a site close to the stimulating electrodes in the potentially intact area, and to another site within the area of potential ischemia at some distance from the site of stimulation. Local electrograms of the potentially intact and ischemic sites, a lead II electrocardiogram and the artifact of stimuli delivered to the stimulating electrodes were all monitored on an Electronics for Medicine recorder. The stimuli were also displayed on an oscilloscope and calibrated by use of a Tektronix current probe amplifier.

The patterns of pacing and test stimuli delivered to the ventricle were programmed by using a variable interval generator and a series of Tektronix wave form and pulse generators. The output of the pulse generator triggered a Grass stimulator which delivered 3 msec pulses to the stimulating electrodes. Ventricular fibrillation threshold was determined by delivering a train of rapid rectangular pulses across the vulnerable period. The method, which was first used by one of us,[2] is depicted in Figure 1. The ventricle was paced by basic stimuli at a cycle length of 400 msec, and the train of rapid pulses was delivered after every 12th basic ventricular response. The pulses were 3 msec in duration and occurred at 10 msec intervals (100/sec). The train was started at about 100 msec after the basic response, and its duration did not extend beyond the absolute refractory period of the premature response evoked by the train. The intensity of the rapid pulses was gradually increased until fibrillation resulted. The fibrillation threshold was then defined as the minimal current in milliamperes that induced fibrillation. Defibrillation was accomplished by direct-current countershock, and 10 to 15 minutes was allowed for recovery before further observations were made.

Results

Figure 2 shows procainamide blood levels plotted against time after a single intravenous injection of the drug in a dose of 10 or 20 mg/kg in five dogs. Only one dog received 20 mg/kg, and the uppermost line indicates the blood levels achieved in this animal.

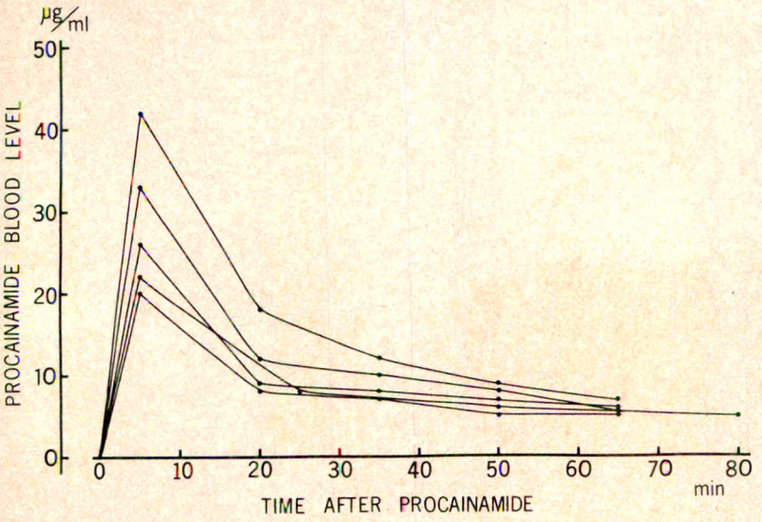

FIGURE 2. Time course of changes in procainamide blood concentration after an intravenous injection of the drug in a dose of 10 or 20 mg/kg in five dogs.

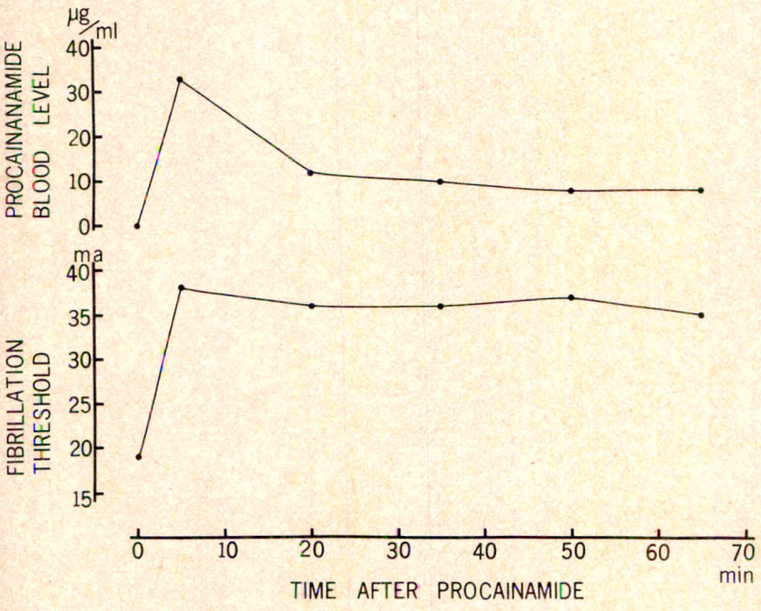

FIGURE 3. Comparison of the time course of changes in procainamide blood concentration and ventricular fibrillation threshold in a dog after an intravenous injection of 10 mg/kg of procainamide.

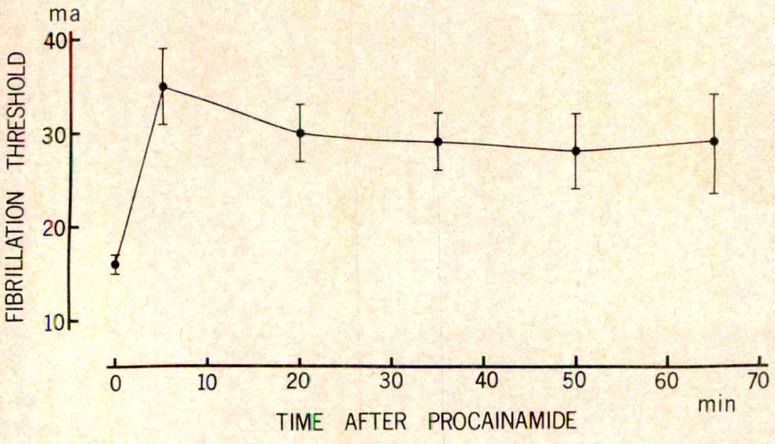

FIGURE 4. Effect of procainamide on the ventricular fibrillation threshold of 12 dogs without acute myocardial ischemia. The values are expressed as means ± standard error at zero time before injection of procainamide and at various times after injection.

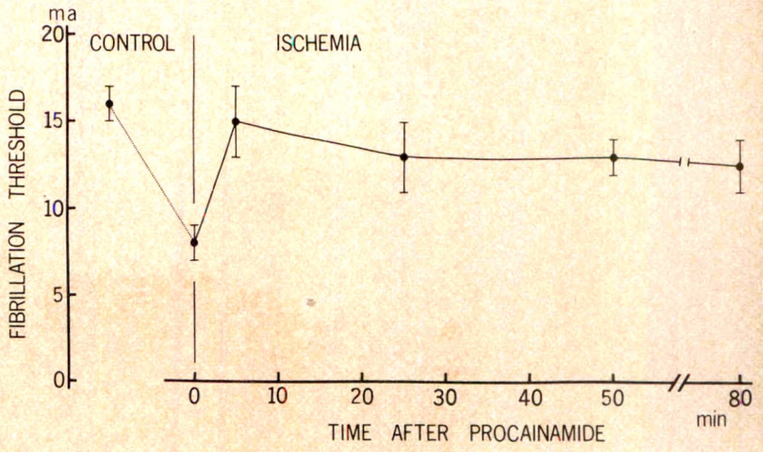

FIGURE 5. Effect of procainamide on the ventricular fibrillation threshold of 11 dogs during acute myocardial ischemia. The control fibrillation threshold is shown at the left. The value at time zero is the fibrillation threshold during acute coronary occlusion before injection of procainamide. The fibrillation thresholds during acute myocardial ischemia are also shown at various times after the injection. The values are expressed as means ± standard error.

The remaining four animals received the drug in a dose of 10 mg/kg. The blood levels were initially high, ranging from 20 to 43 μg/ml 5 minutes after the injection. They fell to therapeutic levels (5 to 10 μg/ml) in 20 to 35 minutes and remained reasonably constant up to 80 minutes after the injection. Procainamide was given in a dose of 10 mg/kg in most of the experiments.

Studies without coronary occlusion: The effect of procainamide on ventricular fibrillation threshold was first studied in 12 dogs without acute coronary ligation. Figure 3 illustrates the results of a representative experiment showing the relation of ventricular fibrillation thresholds to procainamide blood levels. The time course of changes in the fibrillation threshold correlated with changes in procainamide blood levels. The maximal increase in fibrillation threshold occurred at the time of the highest procainamide blood level, 5 minutes after the injection, and an increase in the fibrillation threshold was later maintained at lower values as the procainamide blood concentration remained at therapeutic levels. Figure 4 shows the time course of changes in the mean fibrillation threshold after an injection of procainamide in the 12 dogs without acute coronary occlusion. The mean fibrillation threshold was 16 ma before injection and increased to the maximum of 35 ma 5 minutes after injection ($P < 0.01$). It decreased slightly at 20 minutes, and then remained elevated at 29 to 30 ma up to 65 minutes after the injection ($P < 0.01$). The results indicate that the therapeutic blood concentration of procainamide increased the fibrillation threshold by 14 ma (88 percent) in the ventricles without acute myocardial ischemia.

Studies during acute coronary occlusion: The effect of procainamide on ventricular fibrillation threshold was studied in a group of 11 dogs during acute myocardial ischemia. In these animals, fibrillation thresholds were determined before and during acute ligation of the left anterior descending coronary artery. Procainamide was then injected and the fibrillation thresholds were determined during the coronary occlusion at different intervals from the time of injection. The coronary arterial occlusion lasted for only about 5 minutes before each determination of ventricular fibrillation threshold during acute myocardial ischemia. Figure 5 shows the time course of changes in the mean fibrillation threshold after an injection of procainamide in the 11 dogs during acute occlusion. The mean fibrillation threshold was 16 ma in the control state and decreased to 8 ma during acute occlusion ($P < 0.01$). The mean fibrillation threshold during occlusion was increased to the maximum of 15 ma 5 minutes after injection ($P < 0.01$). It decreased slightly at 25 minutes and then remained elevated at 12 to 13 ma up to 80 minutes after injection ($P < 0.05$). The results indicate that the effect of therapeutic blood levels of procainamide was less pronounced in the ventricles with acute myocardial ischemia than in the control ventricles. The mean increase in ventricular fibrillation threshold in the occlusion studies was only 5 ma (63 percent). In addition, procainamide failed to produce complete reversion of the decreased fibrillation threshold accompanying myocardial ischemia to the control value (16 ma).

Discussion

Procainamide was administered as a bolus injection of 10 mg/kg in most animals in our study. Blood levels of the drug reached their peak immediately, fell to therapeutic levels within about 30 minutes and then remained at those levels as long as the experiment lasted, up to 80 minutes after injection. The dose of procainamide was 20 mg/kg for an initial few experiments, and it resulted in higher therapeutic blood levels of procainamide in these animals. The effect of procainamide on the fibrillation threshold correlated well with procainamide blood levels. The increase, peak and decrease in procainamide blood concentration were paralleled by changes in fibrillation threshold. At therapeutic procainamide blood levels, the mean fibrillation threshold increased markedly from the control value of 16 to 30 ma (88 percent increase) in the normal ventricles.

It has been shown[2,3] that ventricular vulnerability to fibrillation reaches the maximal level at about 5 minutes after occlusion of a coronary artery. We therefore occluded the left anterior descending artery 5 minutes before each determination of ventricular fibrillation threshold. The mean fibrillation threshold decreased markedly from the control value of 16 to 8 ma during acute coronary occlusion (50 percent reduction). The time course of the effect of procainamide on ventricular fibrillation threshold during acute myocardial ischemia was similar to that observed in the normal ventricle. However, the effect was much less pronounced in the ischemic ventricle, and the mean fibrillation threshold increased from 8 to only 13 ma (63 percent increase) at the therapeutic blood concentration of procainamide. Furthermore, procainamide failed to increase the fibrillation threshold above the normal value (16 ma) in the ischemic ventricles at any time after an injection was administered.

Procainamide decreases excitability and responsiveness and increases the effective refractory period of the ventricular muscle.[4] Recent microelectrode studies[5,6] have shown that procainamide decreases automaticity by decreasing the slope of phase 4, decreases conduction velocity by decreasing the rate of phase 0 depolarization, and increases the action potential duration and effective refractory period in the Purkinje tissue. Antiarrhythmic effects of procainamide may be attributed to a decrease in automaticity, a decrease in excitability and an increase in the effective refractory period of the cardiac tissues. The decreased conduction rate may eliminate reentrant beats by the production of bidirectional block in reentrant circuits.[6] The observed increase in ventricular fibrillation threshold may be due to the decreased excitability and prolonged refractory period of the ventricular tissues.

The majority of patients who die of acute myocardial infarction do so suddenly of ventricular fibrillation.[7] Ventricular premature beats are the most frequent arrhythmia observed in patients with acute myocardial infarction, and these premature beats are more likely to initiate ventricular fibrillation during acute myocardial infarction.[7,8] It has been shown[2,9] that ventricular fibrillation threshold is decreased during acute myocardial ischemia in experimental animals, and this was again demonstrated in our study. Procainamide has proved useful in reducing the frequency of ventricular premature beats and fibrillation in patients with acute myocardial infarction. A recent study[7] reported that the drug offers significant protection against ventricular fibrillation in dogs during coronary occlusion.

Our study indicates that procainamide decreases ventricular vulnerability to fibrillation in the ventricle with acute myocardial ischemia, but the effect is relatively less pronounced in comparison with its effect on the normal ventricle. Procainamide was not able to revert the decreased fibrillation threshold accompanying acute myocardial ischemia above the normal value. This is in contrast to the study[1] demonstrating that lidocaine was able to revert the decreased fibrillation threshold well above the normal value during coronary occlusion. In our recent study[10] on the swine model of coronary atherosclerosis produced by the combination of an atherogenic diet and precordial X-irradiation, lidocaine infusion resulted in a four-fold increase in the fibrillation threshold of the ventricles with acute myocardial infarction. These results suggest that lidocaine should offer more effective protection against ventricular fibrillation than procainamide during acute myocardial infarction. The superiority of lidocaine over procainamide in decreasing ventricular vulnerability to fibrillation cannot be clearly explained, but it is possible that lidocaine improves depressed conduction in the Purkinje and ventricular muscle tissues and reduces the likelihood of conduction block and reentry in the ventricle.[11]

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Ventricular Defibrillation in the Dog Using Implanted and Partially Implanted Electrode Systems

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Two totally implanted and two partially implanted electrode systems were studied in 2,100 fibrillation-defibrillation episodes in large anesthetized dogs. In one of the totally implanted systems, two metal disks, 7.6 cm in diameter, were implanted between the pectoralis major muscle and the rib cage, with the right electrode high on the chest and slightly to the right of midline and the left electrode over the apex of the heart. In the other totally implanted system, a unipolar catheter electrode positioned in the right atrium and superior vena cava was used together with a 7.6 cm disk electrode over the apex of the heart. In the partially implanted systems, a unipolar catheter electrode in the right atrium and superior vena cava was used together with either a 7.6 cm disk electrode or a 6.3 by 20.3 cm rectangular sheet electrode placed on the surface of the chest over the apex of the heart. Four types of unidirectional shocks were used in evaluating the twin disk system. Nine types of shocks were used with systems involving the catheter electrode. Derived curves indicate that the 90 percent level of successful defibrillation is achieved with 38 joules on the day of implantation and 54 joules 32 weeks after implantation for the twin disk system, 12 joules on the day of implantation and 19 joules 33 weeks after implantation for the catheter-internal disk system, 15 joules for the catheter-external disk system and 24 joules for the catheter-external sheet system.

The possibility of reducing the incidence of sudden cardiac death by means of automatic standby defibrillation systems that could be implanted in selected patients has been suggested by our own and other groups. Our initial experimental system used electrodes implanted in the chest wall.[1] Mirowski et al.[2] originally visualized a system in which one electrode was incorporated into the tip of a catheter and positioned in the right ventricle and the other electrode was placed under the skin of the anterior chest wall. Later, Mirowski et al.[3] and Denniston et al.[4] proposed an arrangement in which both electrodes were located on a catheter positioned so that one electrode was in the apex of the right ventricle and the other in the superior vena cava. Rubin et al.[5] have suggested a similar scheme. Lown and Axelrod[6] have questioned the validity of pursuing further study of the concept of totally implanted standby defibrillation systems.

Patient and physician acceptance of an automatic standby defibrillator will be dependent upon achieving satisfactory performance with a suitably sized unit. Since the size of the implanted unit is a very strong function of the energy required to achieve defibrillation, we have undertaken detailed studies of the energy requirements for various implanted electrode systems. Previous animal studies by our group have involved bielectrode intravascular catheters in which one electrode is in the right ventricle and the other in the superior vena cava or external jugular vein, or both.[7–9] Our experience has shown

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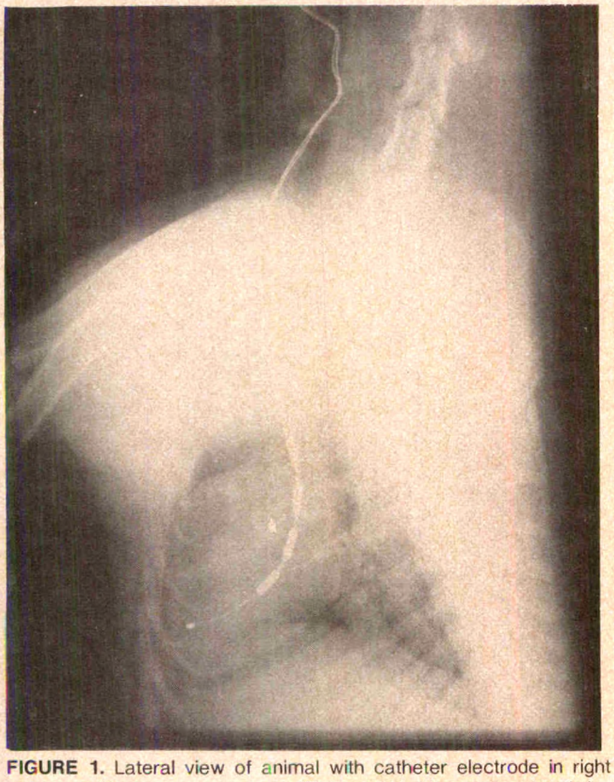

FIGURE 1. Lateral view of animal with catheter electrode in right atrium and superior vena cava. The marker slug at the tip of the catheter is insulated and not a part of the electrode system.

that the effectiveness of such bielectrode catheters in achieving defibrillation is critically dependent upon the tip of the distal electrode remaining well positioned in the apex of the right ventricle. Mirowski et al.[10] have had limited clinical experience with bielectrode catheters having one electrode in the apex of the right ventricle and the other in the superior vena cava.

This paper reports an extensive study of the energy required to achieve defibrillation with two additional types of totally implanted electrode systems. In the first of these systems, two disk electrodes are implanted in the anterior chest wall. In the second system, a catheter having an electrode in the right atrium and superior vena cava is used in conjunction with a disk implanted in the anterior chest wall over the apex of the heart. In addition, two partially implanted systems are considered.

Methods

Implanted Disks

Three dogs ranging in weight from 27 to 31 kg were used. Initially, each animal was subjected to a series of 20 transthoracic fibrillation-defibrillation episodes. An animal was anesthetized with pentobarbital sodium, 27.5 mg/kg body weight, and placed on a thick Plexiglas® table top. Disk electrodes, measuring 7.6 cm in diameter, were covered with Redux paste and taped to the anterior portion of the shaved chest. One electrode was placed over the apex of the heart and the other was positioned slightly to the right of the midline and higher on the chest.

Ventricular fibrillation was then induced by a low current shock and 30 seconds later an effort was made to defibrillate with the wave form being studied. If defibrillation was achieved on the initial trial, the episode was recorded as a success. Otherwise, the event was recorded as a failure and a shock of known high effectiveness was used to salvage the animal. In either event, the procedure was repeated with not less than 3 minutes elapsing between the start of successive episodes. Unidirectional, rectangular wave shocks, 4 msec in duration, were evaluated. In the first group of five episodes, the current amplitude was fixed at 7 amperes. In the second, third and fourth groups of five episodes, the current amplitude was 10, 14 and 20 amperes, respectively. This portion of our study involved 60 fibrillation-defibrillation episodes.

A high power vacuum tube defibrillator, which has previously been described[11] was used to supply all of the shocks. The wave forms of both the current and the voltage associated with the defibrillatory shocks were observed on a Tektronix model 5031 dual beam storage oscilloscope. The electrocardiograms of the animals were observed on a Hewlett-Packard model 130C oscilloscope.

After the initial transthoracic study, stainless steel electrodes 7.6 cm in diameter, polished on one face and insulated with epoxy and silastic on the other face, were implanted between the pectoralis major muscle and the rib cage with the conducting surface toward the rib cage. The right electrode was high on the chest and to the right of the midline. The left electrode was over the apex of the heart. Connections to the disks were made by leads whose proximal ends were externalized at remote locations during each period of evaluation and then reburied.

Using the same test procedure as outlined for our initial transthoracic study, we evaluated the resistance levels and effectiveness of the electrode system in reversing fibrillation in each of the three animals on the day of implantation and 1, 4, 8, 12, 16, 20, 24, 28 and 32 weeks after implantation. A total of 600 fibrillation-defibrillation episodes were used in this portion of our study.

Catheter-Implanted Disk

In two animals with implanted disks, catheters were inserted 33 weeks after the implantation of the disks, first through the right jugular vein and then on another day through the left jugular vein, so as to position an electrode in the right atrium and superior vena cava. The silastic catheter used in our study employed four stainless steel sleeves that were electrically connected together to constitute one electrode. The sleeves were 4 mm in diameter and 15 mm in length and were separated from each other by 10 mm. The most distal sleeve was 50 mm from the tip of the catheter.

In each of our four studies with these two animals, the catheter was inserted through a jugular vein and the tip, as visualized by a marker slug, positioned under fluoroscopy in the apex of the right ventricle. Ties around the vein and catheter, proximal and distal to the site of insertion, served to keep the catheter in position. The same insertion procedure was used in all of our work involving catheters. A typical view, from our catheter-external disk series, is shown in Figure 1.

Nine types of unidirectional rectangular wave shocks were used (5 amperes at 4, 8 and 16 msec, 7 amperes at 2, 4 and 8 msec and 10 amperes at 1, 2 and 4 msec). On a given day, this group of nine shocks was repeated five times. Thus, a given animal on a given day was subjected to 45 fibrillation-defibrillation episodes. The defibrillatory shocks being evaluated were delivered by our vacuum tube defi-

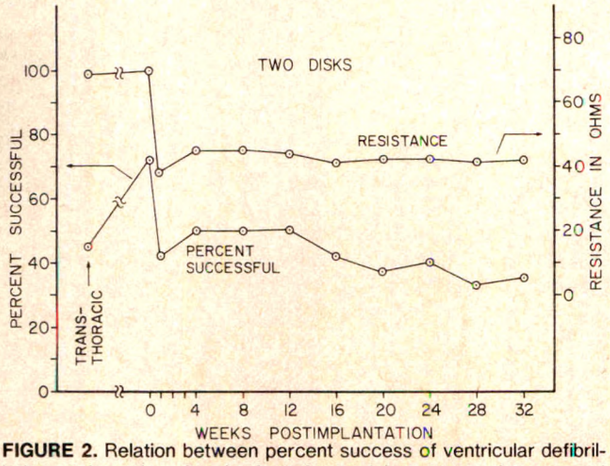

FIGURE 2. Relation between percent success of ventricular defibrillation and weeks after implantation and between resistance and weeks after implantation for implanted disk system when evaluated with set of shocks as specified in text.

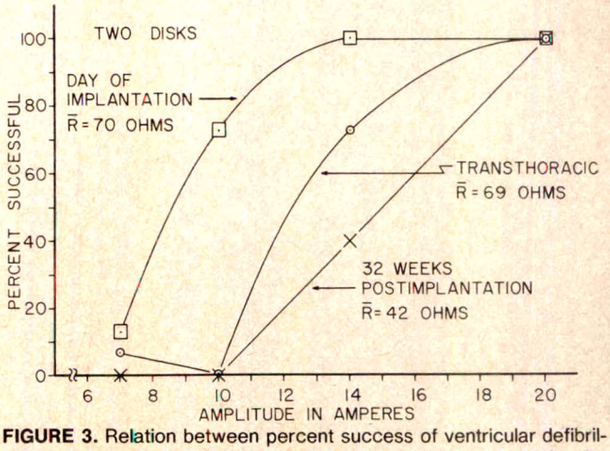

FIGURE 3. Relation between percent success of ventricular defibrillation and amplitude of 4 msec unidirectional rectangular pulse for the twin disk system as evaluated on a transthoracic basis, on the day of implantation and 32 weeks after implantation.

brillator to the electrode system consisting of the catheter electrode in the right atrium and superior vena cava and the disk electrode implanted over the apex of the heart. Shocks for inducing fibrillation and for salvaging the animal in the event the experimental shock was unsuccessful were delivered by another defibrillator[12] to the electrode system consisting of the two implanted disks. The waiting period between the induction of fibrillation and the application of the test shock and the time interval between the start of successive episodes were the same as those in our work with the implanted disks. A total of 180 fibrillation-defibrillation episodes were used in this portion of our study.

In four animals, ranging in weight from 24 to 29 kg, a study of the catheter-implanted disk system was conducted on the same day that a single disk was surgically implanted in the chest wall over the apex of the heart of each of the animals. In this part of the study, the defibrillatory wave forms being evaluated were again delivered to the electrode system consisting of the catheter electrode in the right atrium and superior vena cava and the disk electrode implanted over the apex of the heart. Shocks for inducing fibrillation and for salvaging the animal in the event the experimental shock was unsuccessful were delivered to an electrode system consisting of the implanted disk and an auxiliary disk on the surface of the right side of the chest. Each of these animals was subjected to the same series of 45 fibrillation-defibrillation episodes used in the long-term studies. A total of 180 fibrillation-defibrillation episodes were used in this portion of our study.

Catheter-Surface Disk

The experimental procedure for this portion of our study was substantially the same as that used for our work involving an implanted disk except that external disks were used. The electrode system under study consisted of the catheter electrode in the right atrium and superior vena cava and a 7.6 cm diameter Redux-covered disk electrode taped on the surface of the shaved chest over the apex of the heart. Seven animals ranging in weight from 24 to 29 kg were used. Four of the animals underwent 90 fibrillation-defibrillation episodes each (45 on one day and an additional 45 on another day), and three animals underwent 180 episodes. Thus, the derived data for this portion of our study are based on 540 episodes.

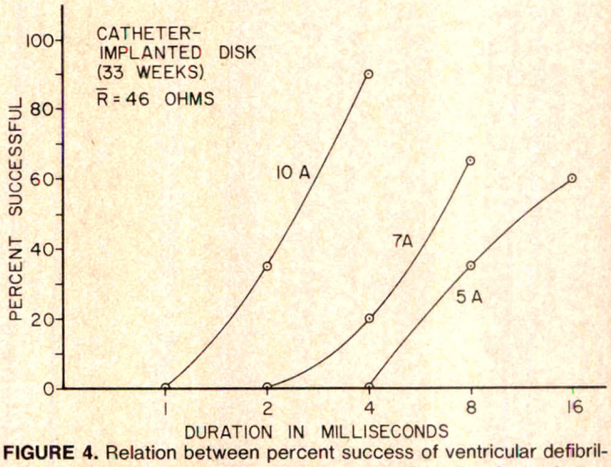

FIGURE 4. Relation between percent success of ventricular defibrillation and duration of unidirectional rectangular pulse for catheter-implanted disk system 33 weeks after implantation.

Catheter-External Sheet

The experimental procedure for this portion of our study was the same as that used in our work involving a surface disk, except that a 6.3 by 20.3 cm rectangular metal sheet was used for the surface electrode. The center of the rectangular sheet was centered over the apex of the heart with the rectangle oriented so that its long axis was perpendicular to the axis of the animal. The seven animals used in 540 episodes ranged in weight from 24 to 28 kg.

Results

The electrode-to-electrode resistance and effectiveness of defibrillation of the implanted disk system are sketched as functions of time and compared to transthoracic results in Figure 2. Each datum point on the resistance curve and each datum point on the percent success curve represents our experience with the complete given set of 20 shocks in each of three animals. Thus, the resistance value and the percent success figure represent the average determined from 60 shocks. Figure 3 shows the relations

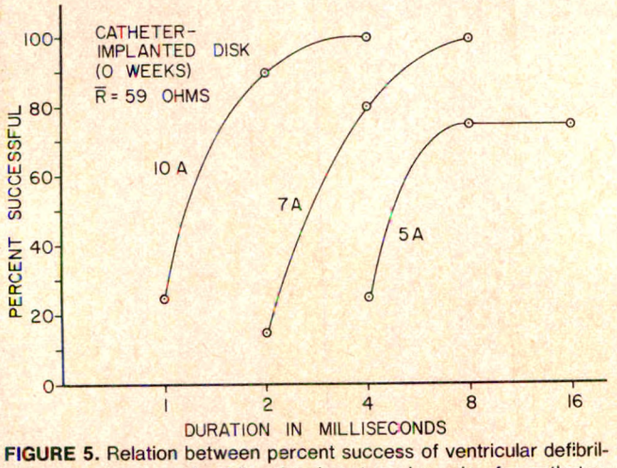

FIGURE 5. Relation between percent success of ventricular defibrillation and duration of unidirectional rectangular pulse for catheter-implanted disk system on day of disk implantation.

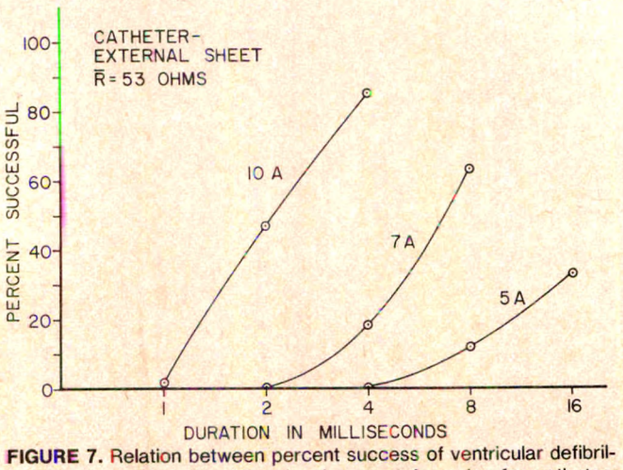

FIGURE 7. Relation between percent success of ventricular defibrillation and duration of unidirectional rectangular pulse for catheter-external sheet system.

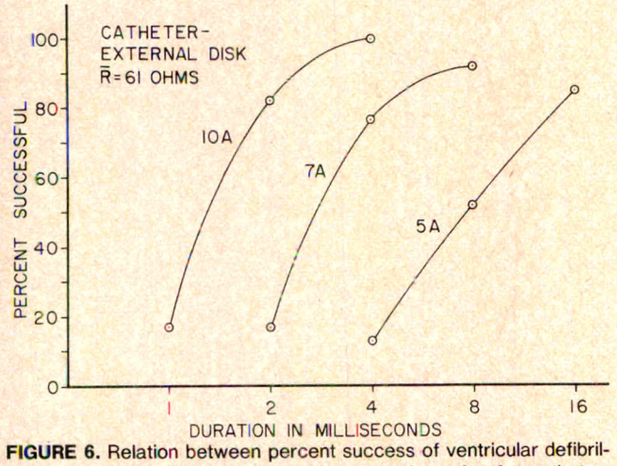

FIGURE 6. Relation between percent success of ventricular defibrillation and duration of unidirectional rectangular pulse for catheter-external disk system.

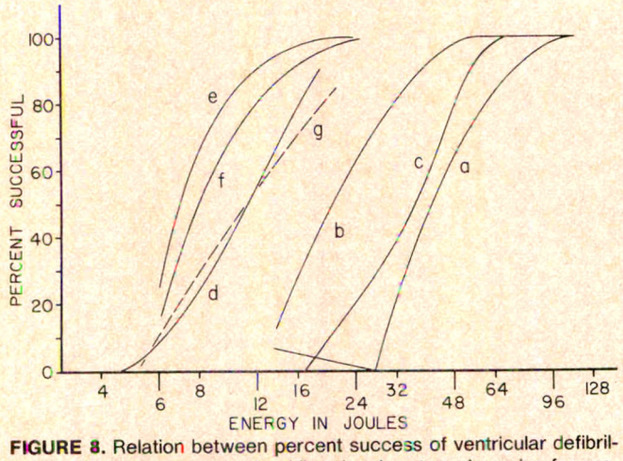

FIGURE 8. Relation between percent success of ventricular defibrillation and energy content of unidirectional rectangular pulse for systems consisting of two disks on surface of chest **(a)**, two implanted disks as evaluated on the day of implantation **(b)**, two implanted disks as evaluated 32 weeks after implantation **(c)**, catheter-implanted disk as evaluated 33 weeks after implantation **(d)**, catheter-implanted disk as evaluated on day of disk implantation **(e)**, catheter-surface disk **(f)** and catheter-surface sheet **(g)**.

between percent effectiveness and amplitude of the 4 msec shocks on a transthoracic basis, just after implantation and 32 weeks after implantation. Each datum point is based on 15 episodes, 5 in each of three animals. The average resistance associated with each of the three curves is also indicated.

Figures 4 through 7 summarize our results for the systems that involve an electrode in the right atrium and superior vena cava in conjunction with implanted or surface disks or a surface sheet electrode. In Figures 4 and 5, each datum point reflects our experience in 20 fibrillation-defibrillation episodes. In Figures 6 and 7, each datum point is based on 60 episodes. Average resistance values are indicated on each figure.

The energy content in joules of a unidirectional rectangular wave shock is given by the equation $U = I^2RT$, where I is the current in amperes, R the resistance in ohms and T the duration of the shock in seconds. Using this relation, we replotted in Figure 8 the three curves of Figure 3 and the 10 ampere members of each of the families of curves of Figures 4 through 7 so as to show the percent success as a function of the energy content of the shock.

Discussion

It is apparent from the data of Figure 2 that the effectiveness of defibrillation increases significantly as the disk electrodes are moved from the surface of the chest to the rib cage. We consider that this initial increase in effectiveness is probably due to an improvement in the flow pattern of the current, with a larger portion of the total current passing through the heart when the disks are on the rib cage. During the first week the disks are implanted, there is a very significant reduction in both resistance and defibrillation

effectiveness. We hypothesize that the decrease in resistance is due to the development of a high conductivity region in the biological material immediately surrounding each disk and that this in turn causes a more diffused flow pattern of current. The data presented in Figures 2 and 3 indicate that the effectiveness of defibrillation 32 weeks after implantation is somewhat less than that 1 week after implantation and much less than that on the day of implantation.

For the catheter-disk systems, the data in Figures 4 through 6 show a significant increase in system effectiveness as the disk is moved from the surface of the chest to the rib cage and then a marked decrease in effectiveness 33 weeks after implantation compared to effectiveness on the day of implantation. The average resistance of the catheter-disk systems decreases very slightly as the disk is moved from the external surface of the chest to the rib cage and then decreases significantly 33 weeks after implantation. This sequence of events is the same as that observed for the twin disk system, and we attribute it to the same factors. Our hypothesis concerning the relation between effectiveness and the flow pattern of the current is further strengthened by the observation that the results for the catheter-external sheet system (Fig. 7) are very nearly the same as for the catheter-implanted disk system 33 weeks after implantation (Fig. 4). With use of the equation cited previously, it is evident that on an energy content basis, the 10 ampere members of each of the families of curves in Figures 4 through 7 are superior to the 7 and 5 ampere members of the same family. This is the reason why these curves were selected for replotting on an energy basis in Figure 8.

The most significant single feature of the family of curves shown in Figure 8 is that any given percent success level can be achieved with significantly less energy in systems involving the right atrium—superior vena cava electrode (curves d, e, f and g) than with twin disk systems (curves a, b and c).

Although exactly comparable data are not available for the bielectrode catheter having one electrode in the apex of the right ventricle and the other in the superior vena cava or jugular vein, or both, available data [7–9] suggest that the energy requirements for the right atrium and superior vena cava-implanted disk system (curves d and e, Fig. 8) compare favorably with the requirements for the bielectrode catheter.

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Accelerated Cardiac Escape Rhythms Caused by Ouabain Intoxication

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In anesthetized dogs treated with ouabain, the ventricular escape intervals were measured after (1) vagally induced atrioventricular block, (2) ventricular premature stimulation, or (3) cessation of a period of regular pacing at various cycle lengths. The escape intervals were a direct function of the basic cycle length and were significantly influenced by the last cycle length, whether premature or postmature. Postpacing acceleration of atrial ectopic responses was also demonstrated. When compared with results obtained in isolated Purkinje tissue, ectopic activity associated with early ouabain toxicity appears to be caused by frequency-related transient depolarizations rather than "true" phase 4 depolarization.

Ectopic ventricular activity accompanying digitalis intoxication is usually attributed to the development of pacemaker activity within the specialized conduction system of the ventricles. So long as the intrinsic frequency of the ectopic focus remains slower than that of the sinoatrial node, its pacemaker potentiality remains silent. During the "silent" period, ectopic activity may be exposed by vagal stimulation.[1] The ventricular "escape" interval during vagal stimulation has often been used as an indicator of developing digitalis intoxication in experimental preparations.[2]

If an accelerated ectopic pacemaker can be exposed during the pause induced by vagal stimulation, it should also escape during the compensatory pause after a premature ventricular contraction; and this, too, has been demonstrated. Castellanos et al.[3] observed repetitive responses to single pacemaker stimuli applied to the ventricle during diastole. Lown et al.[4] applied the term repetitive ventricular response ("RVR") to this phenomenon and suggested that it might be used as a sensitive indicator of digitalis intoxication. In their experiments, it seemed clear that a ventricular ectopic focus emerged during the compensatory pause after a premature beat and that, depending upon the relative frequencies of the normal and ectopic pacemakers, "interference dissociation" could permit a series of extrasystoles to appear. If this explanation were valid, one would expect reduction of the sinoatrial nodal frequency by vagal stimulation to expose the same ectopic pacemaker at the same escape interval and frequency. However, Vassalle et al.[5] observed that ventricular extrasystoles appearing during ouabain intoxication were suppressed when the sinus rate was slowed, whereas acceleration resulted in runs of extrasystoles. Wittenberg et al.[6,7] also demonstrated that a period of rapid pacing enhanced the idioventricular frequency.

In preliminary studies, we observed that (1) the escape intervals characteristic of the repetitive ventricular response phenomenon were briefer than those that occurred during vagal stimulation, and (2) the site of origin of the ectopic activity was very often different. These observations were obviously incompatible with the idea that an occult pacemaker will escape whenever a long enough interval is pro-

From the Masonic Medical Research Laboratory, Utica, N. Y. and the Krannert Institute of Cardiology, Indianapolis, Ind. This study was supported in part by a grant from the Central New York Heart Association, and the Indiana Heart Association. Manuscript accepted July 5, 1973.

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vided. Our findings suggested that the effects of vagal stimulation and premature ventricular stimulation are at least quantitatively different.

During the course of our preliminary studies, Ferrier et al.,[8] examining the effects of acetylstrophanthidin on isolated Purkinje fibers, observed the development of frequency-dependent transient depolarizations during a pause after a series of driven responses. These depolarizations could reach threshold levels and cause one or more automatic responses. Ferrier et al. concluded that the transient depolarizations, rather than "true" phase 4 depolarization, were responsible for early ectopic activity induced by the cardiac glycosides.

The in vitro observations in isolated Purkinje tissue appeared to fit the characteristics of several phenomena: repetitive ventricular response, frequency-dependent extrasystolic activity and vagally induced escape beats under the influence of cardiac glycosides. The studies reported here were undertaken to analyze these phenomena and to relate them to the in vitro observations of Ferrier et al.[8]

Methods

The study was performed in 36 adult mongrel dogs of both sexes, anesthetized with pentobarbital sodium, 30 mg/kg, and ventilated with a Harvard respirator. The chest was opened in the midline and the pericardium was used to support the heart. In some experiments the sinus node was crushed to achieve a slower spontaneous heart rate. The vagi were isolated and cut in the neck, and the distal ends were used for stimulation. Stimulating and recording bipolar hook electrodes with an interelectrode distance of 1 to 2 mm were placed on the atria and ventricles. Stimuli of 2 msec duration were delivered through an isolated circuit by a Tektronix pulse generator, triggered by a digitally controlled interval generator, at an intensity of 1 1/2 times the diastolic threshold. After demonstration of failure of accelerated ventricular escape beats to emerge during the control period, 25 μg/kg of ouabain was administered intravenously and testing was repeated. If necessary, subsequent injections of ouabain (10 μg/kg at 1/2 to 1 hour intervals) were made until escape beats occurred. Testing for escape beats was begun about 5 minutes after each dose; more extensive series of observations were made when escape intervals were stable, 20 to 30 minutes after injection of ouabain.

During continuous atrial pacing, accelerated ventricular escape beats were elicited by two methods. Premature stimuli were delivered to the ventricles as in the studies of Lown et al.;[4] this maneuver allowed an accelerated ventricular escape beat to occur during the compensatory pause after the premature ventricular complex (Fig. 1, A and B). The second method employed vagal stimulation for 50 msec with square wave pulses of 1 to 2 msec duration at a frequency of 40 to 80 Hz delivered 150 msec before the next atrial stimulus (Fig. 1C). The voltage was adjusted to cause atrioventricular block of a single atrial paced impulse without affecting atrioventricular conduction of succeeding responses. On occasion, combinations of premature ventricular stimulation and vagal stimulation were employed. In some experiments, regular pacing and premature stimuli were applied to the ventricle; vagal stimulation was continuous to prevent interference from supraventricular pacemakers. Ventricular escape intervals were measured from

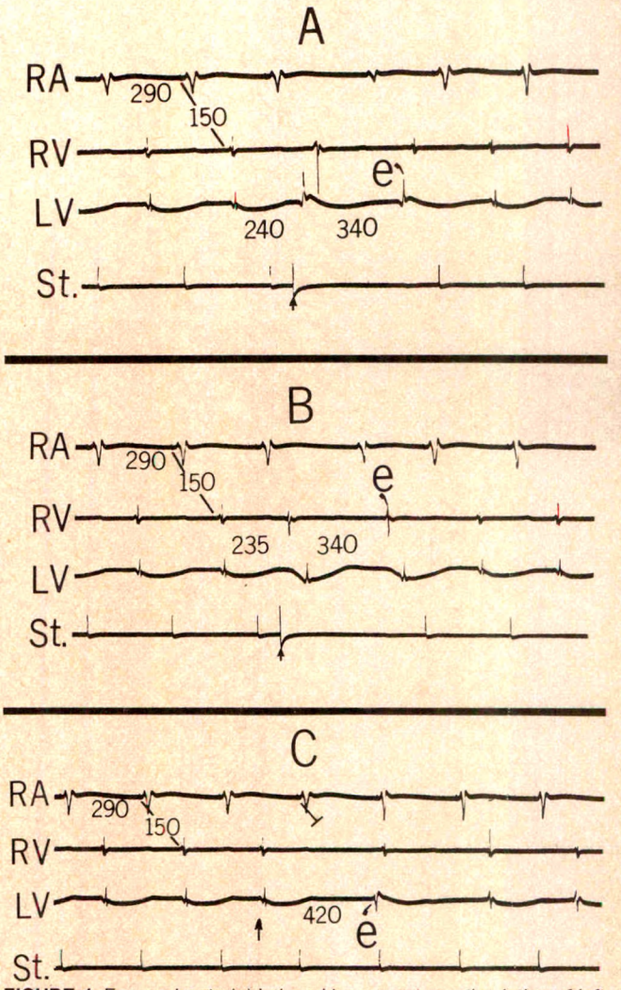

FIGURE 1. Escape beats (e) induced by premature stimulation of left ventricle **(A)**, right ventricle **(B)** and vagus **(C)**. The right atrium is driven at a basic cycle length of 290 msec in all panels. Tracings, top to bottom: right atrial (RA), right ventricular (RV) and left ventricular (LV) electrograms and stimulus artifact (St). The coupling interval of the left ventricular premature response in **A** is 240 msec; that of the right ventricular premature response in **B** is 235 msec. Escape intervals in **A** and **B** are 340 msec; the escape beat originates in the stimulated ventricle in each case. In **C**, a brief burst of vagal stimuli (at **arrow**) blocks transmission of next atrial response, permitting a left ventricular escape beat at 420 msec.

the local electrograms of the ventricular escape beats, recorded at a paper speed of 100 mm/sec on a multichannel oscillograph.

The effects of rapid atrial pacing upon atrial rhythm were evaluated by driving the atrium rapidly at different frequencies for 30 seconds and suddenly terminating pacing. These experiments were performed in animals with a crushed sinoatrial node. The initial escape interval was determined by measuring the interval between the electrogram of the atrial escape beats and the electrogram from the last atrial paced beat.

Results

General Nature of the Escape Beats

Ventricular escape beats could be demonstrated as early as 20 minutes after the intravenous administra-

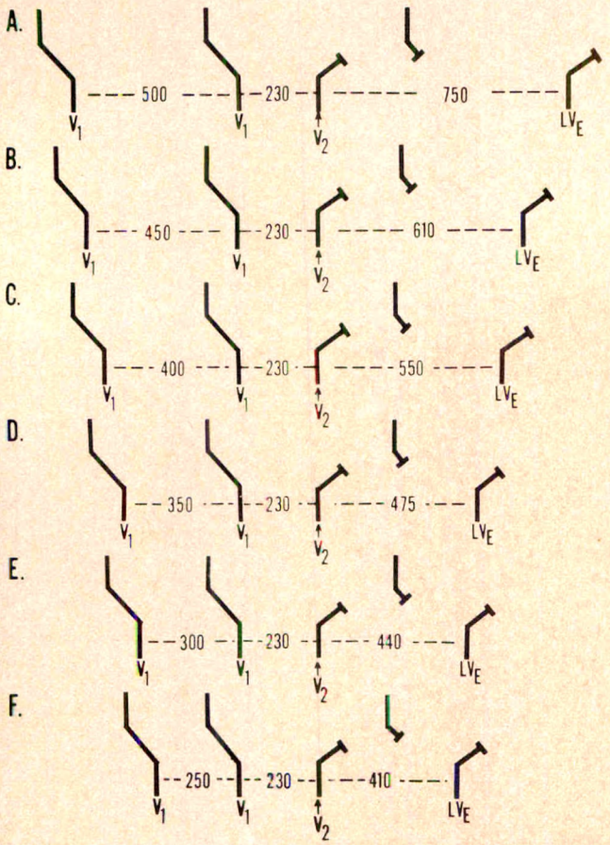

FIGURE 2. Effect of basic cycle length on escape intervals after premature stimulation of the left ventricle. The atrium was paced at the cycle lengths (in milliseconds) indicated in the column at **left;** the V_1–V_2 interval is fixed at 230 msec. LV_E = left ventricular escape beats at the intervals listed in the column at **right.**

tion of 25 μg/kg of ouabain, at a time when there were no overt signs of ectopic activity. In 3 of 14 dogs, premature ventricular stimulation resulted in coupled ventricular responses (repetitive ventricular response) at a stage when vagal stimulation failed to elicit an escape beat within the interval provided; the reverse situation occurred in 2 dogs. In nine dogs, ventricular escape beats could be produced at the same level of ouabain intoxication by either premature ventricular stimulation or vagal stimulation; however, shorter driving cycle lengths were frequently necessary to produce vagally induced escape beats.

Figure 1 illustrates the testing procedure. The atria were driven at a cycle length of 290 msec for 8 to 10 basic cycles. Early premature stimuli applied to the left or right ventricle resulted in coupled beats at an escape interval of 340 msec (Fig. 1, A and B). Vagal stimulation (Fig. 1C, arrow) blocked a single P wave; in the ensuing pause, a left ventricular escape beat occurred at a cycle length of 420 msec.

Mechanism of vagally induced escape beats and repetitive ventricular response: Two features of this experiment suggested that the vagally induced escape beat and the repetitive ventricular response might represent two different mechanisms. The repetitive ventricular response appeared at a shorter interval than the vagally induced escape beat, and in each case originated within the ventricle that was stimulated. If the ectopic responses represented the activity of a latent pacemaker permitted to emerge by the compensatory pause (Fig. 1,A and B) or by the vagally induced atrioventricular block (Fig. 1C), the same escape interval and the same configuration of the ectopic response should have occurred in each case.

At this stage in the study, it was considered possible that a latent pacemaker within the more proximal distribution of the conduction system might be temporarily inhibited by vagal stimulation. However, vagal stimulation sufficient to block atrioventricular transmission during atrial pacing resulted in escape intervals similar to those that followed simple cessation of atrial stimulation. We concluded that the vagus nerve did not significantly influence discharge of the ectopic pacemaker.

Effect of Heart Rate

Experiments were devised to test the influence of basic frequency on the escape interval. In one set of observations, the V_1–V_2 response interval for the premature response was held constant while the basic cycle length was altered; in the other set, the driving frequency was constant while the V_1–V_2 interval was altered.

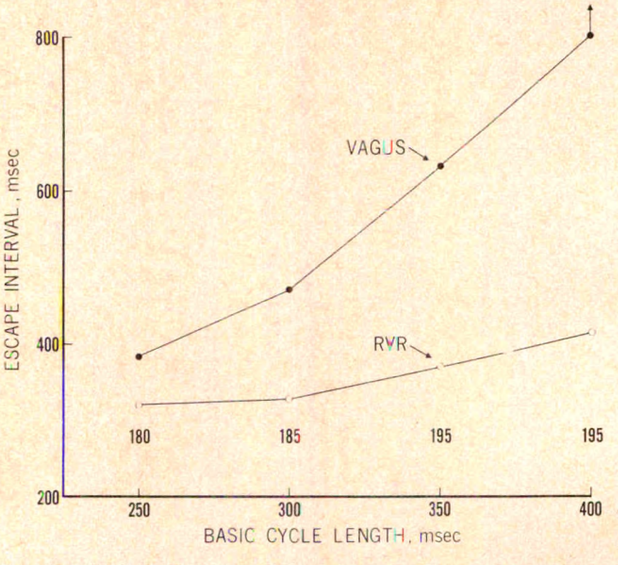

FIGURE 3. Left ventricular escape intervals exposed by vagal stimulation **(solid circles)** and by early premature stimulation of the left ventricle (**open circles,** RVR, "repetitive ventricular response") as a function of basic cycle length. The heart is driven by atrial stimuli. V_1–V_2 intervals are shown at each basic cycle length indicated by the row of figures at bottom. **Upright arrow** at basic cycle length = 400: no escape occurs within the 800 msec interval provided.

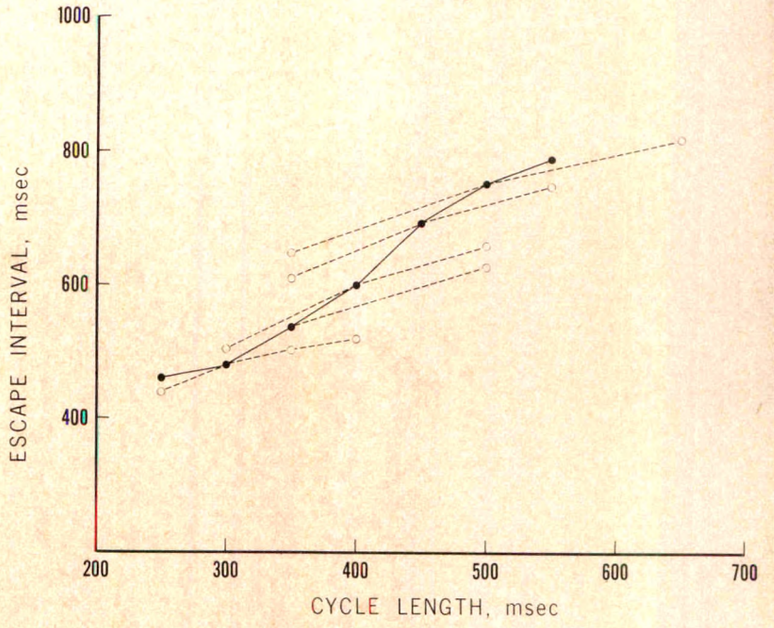

FIGURE 4. Cumulative effect of cycle length on escape interval. The **solid line** connects points recorded after interruption of the train of driving stimuli, at indicated cycle lengths. **Broken lines** indicate premature and postmature stimuli at various basic cycle lengths.

The escape interval after a premature ventricular stimulus at a fixed V_1–V_2 interval is, like the vagally induced escape interval, a function of the basic cycle length preceding the V_2 stimulus. In the experiment illustrated in Figure 2 the V_1–V_2 interval was fixed at 230 msec, and the premature stimulus was applied to the right ventricle. The escape beat, originating in the left ventricle, occurred progressively earlier as the basic cycle length was reduced from 500 to 250 msec.

In the other set of experiments, the basic cycle length was fixed as the V_1–V_2 interval was increased. The escape interval increased progressively as a function of the V_1–V_2 interval.

Comparison of escape intervals resulting from premature and vagal stimulation: Figure 3 compares the escape intervals resulting from premature stimulation and those exposed by vagal stimulation. Both sets of data were obtained from the same animal at approximately the same time. The heart was driven by rhythmic stimuli applied to the right atrium at cycle lengths of 400 to 250 msec. Premature stimuli were applied to the left ventricle at the end of the functional refractory period. At the same basic cycle lengths, atrioventricular block of a single atrial response was induced by brief bursts of stimuli applied to the vagus nerves 150 msec before the subsequent atrial discharge. At the slowest frequency no vagally induced escape beat appeared within the 800 msec pause allowed, but premature ventricular stimulation induced a left ventricular escape beat at 415 msec. At faster driving rates, the vagally induced escape interval was always longer than the repetitive ventricular response interval. Similar relations were observed in other experiments.

If the escaping focus is the same whether exposed by vagal or premature ventricular stimulation, and if its intrinsic rate is not altered by vagal discharge, then the vagally induced escape interval represents the cumulative effect of the driving frequency, and the downward displacement of the repetitive ventricular response curve represents the additional influence of the last (premature) cycle length.

Effect of basic driving frequency on escape interval: The cumulative effect of the basic driving frequency is defined in Figure 4. In this experiment, the heart was driven by stimuli applied at various frequencies to the right ventricle. Interference from supraventricular pacemakers was suppressed by vagal stimulation. After each train of 10 driving stimuli, the stimulator was interrupted long enough to define the relation between basic cycle and escape interval. At each driving rate, an early premature stimulus was delivered through the same stimulating electrodes, and the now briefer escape interval was recorded. Similarly, the response to postmature stimuli ($S_1S_2 > S_1S_1$) was recorded.

The data in Figure 4 describe a kind of hysteresis loop; there is a cumulative effect of the basic driving frequency on the escape interval, but the last cycle, whether briefer or longer than the basic cycle, exerts a major influence.

Atrial Escape Rhythms

The effect of ouabain on ectopic activity in the atria was evaluated by using the technique of "overdrive" pacing in animals with a crushed sinus node. The atrium was driven at various frequencies for a period of 30 seconds, and the subsequent escape interval was recorded. It was established in each case that the first spontaneous response was not a ventricular escape beat propagated back to the atrium, but its precise site of origin was not determined. Figure 5

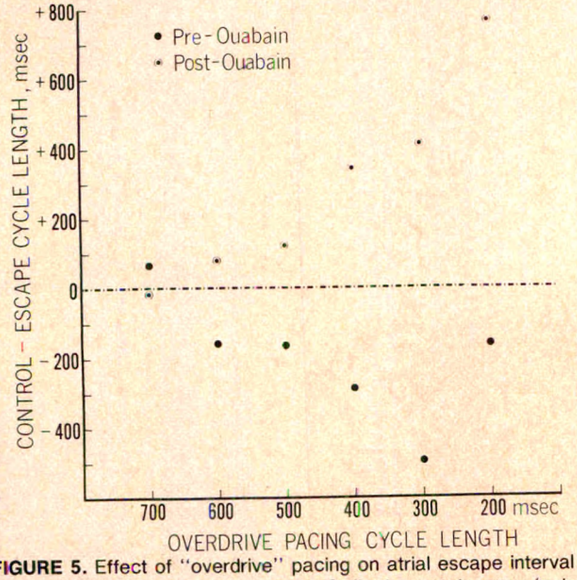

FIGURE 5. Effect of "overdrive" pacing on atrial escape interval in an animal with a crushed sinus node. **Ordinate:** spontaneous (ectopic) atrial cycle length minus escape interval. **Abscissa:** cycle length of overdrive pacing of the atrium for 30 second periods. The upward "displacement" of the control data point at the 200 msec cycle length probably represents a 2:1 response of the ectopic pacemaker site to the pacing stimuli.

illustrates one such experiment. Before administration of ouabain, the spontaneous prepacing cycle lengths ranged from 700 to 1,100 msec. After administration of ouabain, the spontaneous frequency was slightly depressed; the cycle lengths ranged from 950 to 1,200 msec. To "normalize" the escape intervals, the data are plotted as the difference between the spontaneous prepacing cycle length and the first escape interval at each of six driving frequencies. The difference was positive if postpacing acceleration occurred; it was negative if depression resulted. During the control period, the expected postpacing depression of automaticity occurred (filled circles). After the administration of ouabain (45 μg/kg, given intravenously as an initial dose of 25 μg/kg followed by two 10 μg/kg injections at 40 to 60 minute intervals), postpacing acceleration of the atrial escape rhythm was demonstrated.

Discussion

Our experiments confirm the observations of other investigators[3,4,6], who established that an increase in pacing rate accelerated the rate of the postpacing ventricular rhythm and shortened both the first escape cycle length and the escape interval after premature ventricular stimulation. In addition to the basic heart rate, the coupling interval at which a premature stimulus is delivered affects the subsequent ventricular escape interval. Lengthening the coupling interval lengthened the ventricular escape interval until a ventricular escape beat was prevented by the next response of supraventricular origin. A ventricular escape beat could be exposed once again if the spontaneous atrial systole was blocked or delayed. Postmature ventricular stimulation significantly delayed the ventricular escape interval.

At similar basic cycle lengths, ventricular escape intervals that followed vagal stimulation were almost always longer than those that followed premature ventricular stimulation; often, ventricular escape beats followed premature ventricular stimulation, but not vagal stimulation, within the time intervals allotted. The short cycle produced by premature ventricular stimulation, which was not present after vagal stimulation, accounts for these differences. Hagemeijer and Lown[9] also noted that the minimal heart rate necessary to produce ventricular escape beats after premature ventricular stimulation was less than that required to produce escape beats after a pause in pacing.

Mechanisms of Ectopic Activity Associated with Ouabain Toxicity

Kastor et al.[10] suggested that ouabain preferentially enhances automaticity of canine Purkinje fibers in the left ventricle. Rothberger and Winterberg[1] drew a similar conclusion. Our data in part support this conclusion by demonstrating left ventricular escape beats after vagal stimulation in 9 of 14 animals. However, after premature ventricular stimulation, the escape impulse most often arose on the stimulated side. The explanation for this apparent discrepancy is obvious. When a premature response is evoked by a stimulus applied to the right ventricle, any potential ectopic focus within the conducting system on the right will be discharged earlier than a comparable focus on the left. Accordingly, the response will be more premature on the right side, and the coupling interval of the ectopic response within the right ventricle should be correspondingly more abbreviated than in any potential focus on the left side.

Reentry?: The ectopic responses initiated by premature stimulation of the ventricles have usually been considered manifestations of pacemaker activity accelerated by digitalis; closely coupled responses have been ascribed to reentry. However, coupled activity is an early manifestation of digitalis toxicity; it can be demonstrated shortly after the injection of 25 percent of the lethal dose of ouabain, before any significant depression of conductivity in the atrium, atrioventricular node or ventricles. It is unlikely, therefore, that the spontaneous discharge is due to reentry.

Phase 4 depolarization?: It is also unlikely that the ectopic activity results from enhanced phase 4 depolarization, unless that term is broadened to include all automatic activity not due to reentry. In some of the experiments described by Vassalle et al.,[5] the vagal escape interval was prolonged by digitalis, although coupled responses could still be elicited. In the in vitro studies of Ferrier et al.,[8] the "pacemaker" potential of isolated Purkinje fibers was regularly de-

pressed by acetylstrophanthidin at a time when transient depolarizations were coupled to an antecedent driven response. The coupling interval of the transient depolarizations (or ectopic responses generated by them) was abbreviated by acceleration of the driving rate or by the interpolation of premature responses. These events were also described in specialized atrial fibers, identified by the phase 2 plateau configuration of their action potentials.[11]

Rate-dependent depolarizations?: Our results do not permit the conclusion that ectopic activity exposed by vagal stimulation or premature stimulation of the ventricles, or accelerated by increasing the driving rate of the atria or ventricles, is—or is not—due to enhanced phase 4 depolarization. They do not permit arbitrary rejection of reentry as the cause. However, the similarity of the behavior of the ectopic activity with that described by Ferrier et al.[8] and Hashimoto and Moe[11] suggests that the escape responses in the atria and ventricles may be manifestations of rate-dependent transient depolarizations rather than of reentry or "true" pacemaker activity.

Acknowledgment

We acknowledge with thanks the participation of Mr. Frank Kroboth in some of the experiments. We also gratefully acknowledge the technical assistance of Mrs. Anna Malozzi and Miss Claudia Cox.

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Predominant Right Ventricular Dysfunction After Right Ventricular Destruction in the Dog

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Right and left ventricular function was assessed by observing the response to rapid blood volume expansion before and after extensive cauterization of the right ventricle in open chest dogs. In the control period, left ventricular end-diastolic pressure surpassed right ventricular end-diastolic pressure by an average of 11.5 mm Hg after volume expansion whereas, after destruction of the right ventricle, pressure in this chamber surpassed pressure in the left ventricle by an average of 4 mm Hg. In contrast, after left ventricular damage, left ventricular end-diastolic pressure averaged 25 mm Hg more than right ventricular end-diastolic pressure. Despite extensive damage to the right ventricular free wall, the right ventricle continued to generate a near normal pressure and aortic flow could be increased above control levels by volume expansion. We conclude that, in contrast to previous evidence, damage to the right ventricle produces a syndrome of predominant right ventricular dysfunction. However, cauterization of the entire free wall of the right ventricle does not reproduce the more profound right ventricular dysfunction noted in infarction of the right ventricle in man.

Since the original observations of Starr et al.[1] in 1943 that right ventricular damage did not lead to increased venous pressure, it has generally been held that normal right ventricular myocardial function is not necessary for circulatory stability when the pulmonary vascular bed is normal. This thesis has not been reexplored in recent years, nor has it previously been tested clinically because the isolated case reports of right ventricular infarction have not included pertinent hemodynamic observations.

Our recent observation of six patients with apparent right ventricular infarction associated with evidence of predominant right ventricular dysfunction[2] led us to return to the experimental model used by previous workers[1,3,4] in order to define changes in ventricular function more carefully than was possible in the earlier studies. Our findings confirm clinical observations that right ventricular damage may lead to a syndrome of predominant dysfunction of the right ventricle. However, they demonstrate that isolated right ventricular damage should not precipitate a low output state so long as intravascular volume is adequately expanded.

Methods

Eight mongrel dogs were anesthetized with pentobarbital sodium; pulmonary ventilation was maintained by an intermittent positive pressure respirator. The chest was opened by a midsternal incision and the pericardium cut to expose the heart. Catheters were introduced in the femoral artery for continuous monitoring of pressure and in the femoral vein for volume loading and blood withdrawal. The right and left ventricles were catheterized and right and left ventricular end-diastolic pressures were measured from the mid-chest using Statham P23Db strain gage transducers amplified and recorded on a multichannel Hewlett Packard recorder. Aortic flow was mea-

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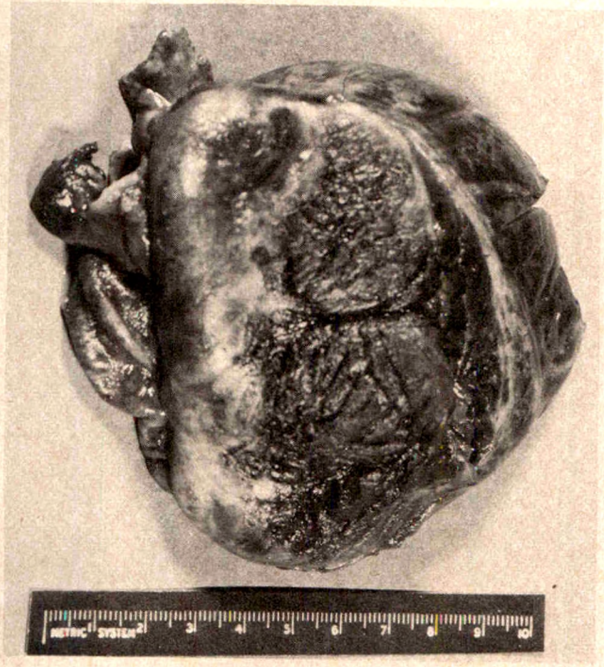

FIGURE 1. Right ventricular free wall after extensive cauterization. Damage extends through entire ventricular wall.

sured by means of an electromagnetic flow probe (Statham) placed around the ascending aorta. Flow was not calculated in absolute terms but was reported as percent change from control levels.

Ventricular damage was produced in seven dogs by application of a heat cautery to the entire free wall of the right ventricle in six dogs and to the anterolateral wall of the left ventricle in one dog. The desired degree of transmural damage—approximately 75 percent of the right ventricular surface (Fig. 1) or 50 percent of the left ventricular surface—was produced by repeated application of the cauterization over approximately 45 minutes until the integrity of the ventricular wall appeared threatened. In the eighth dog left ventricular damage was accomplished by injection of 0.2 ml of mercury into the left circumflex coronary artery. Two dogs died of ventricular fibrillation during the procedure; five other dogs manifested ventricular fibrillation that was promptly reverted by electrical countershock. After the right ventricle had been cauterized, the chamber was noted to be dilated. No systolic contraction of the free wall of the ventricle could be detected visually.

Ventricular function was assessed before and after myocardial damage by monitoring the response to rapid volume expansion. In the control period 500 to 1,000 ml of dextran and saline solution was administered intravenously over a period of 5 to 10 minutes or until left and right ventricular filling pressures were significantly increased. Blood was then withdrawn until ventricular end-diastolic pressures were restored to control levels. Immediately after satisfactory myocardial damage had been produced, the withdrawn blood was rapidly reinfused and additional dextran and saline administered if necessary to raise ventricular end-diastolic pressures to high levels. In two dogs volume expansion was carried out only after right ventricular damage had been produced in order to rule out any possible influence of the precautery volume expansion on the results noted after right ventricular damage. In one dog the circulating blood volume was allowed to equilibrate with a dextran-filled 500 ml reservoir connected in series to the femoral vein before the control studies. Volume loading could then be accomplished without altering the hematocrit by compressing the reservoir to empty its contents into the vascular system.

Results

Ventricular Filling Pressures

After instrumentation of these open chest dogs left ventricular end-diastolic pressure averaged 6.5 mm Hg and right ventricular end-diastolic pressure 2.6 mm Hg (Table I). During rapid volume expansion both pressures increased progressively, with end-diastolic pressure in the left ventricle increasing at a greater rate than that in the right. At the end of the volume infusion left ventricular end-diastolic pressure remained more than double the simultaneously measured right-sided pressure. The response to whole blood expansion from a reservoir was identical to the response to dextran infusion and the data were therefore pooled.

After cauterization of the right ventricle, both right and left ventricular end-diastolic pressures remained normal. However, that in the right ventricle had increased slightly to 5.3 mm Hg and now was slightly greater than that in the left ventricle, which had decreased to an average of 5.0 mm Hg. During rapid volume expansion after right ventricular damage, right ventricular end-diastolic pressure increased at a greater rate than left ventricular end-diastolic pressure (Fig. 2 and 3). At the end of the infusion of blood and dextran, right surpassed left ventricular end-diastolic pressure by an average of 4 mm Hg. The response to the infusion was similar whether the animals had or had not received a volume challenge before cauterization.

Calculation of right ventricular peak systolic minus end-diastolic pressure provided an index of the pres-

TABLE I

Effect of Acute Blood Volume Expansion on Right and Left Ventricular End-Diastolic Pressures (mm Hg) in Open Chest Dogs (means ± standard error of the mean)

	RVEDP	LVEDP
Normal (6 dogs)		
Control	2.6 ± 1.0	6.5 ± 0.5
Volume load	10.5 ± 2.0	22.0 ± 4.3
RV damage (4 dogs)		
Control	5.0 ± 0.8	5.3 ± 1.2
Volume load	21.0 ± 2.3	17.0 ± 3.1
LV damage (2 dogs)		
Control	8.5 ± 0.5	17.0 ± 0.7
Volume load	15.0 ± 0.7	40.0 ± 2.8

LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; RV = right ventricular; RVEDP = right ventricular end-diastolic pressure.

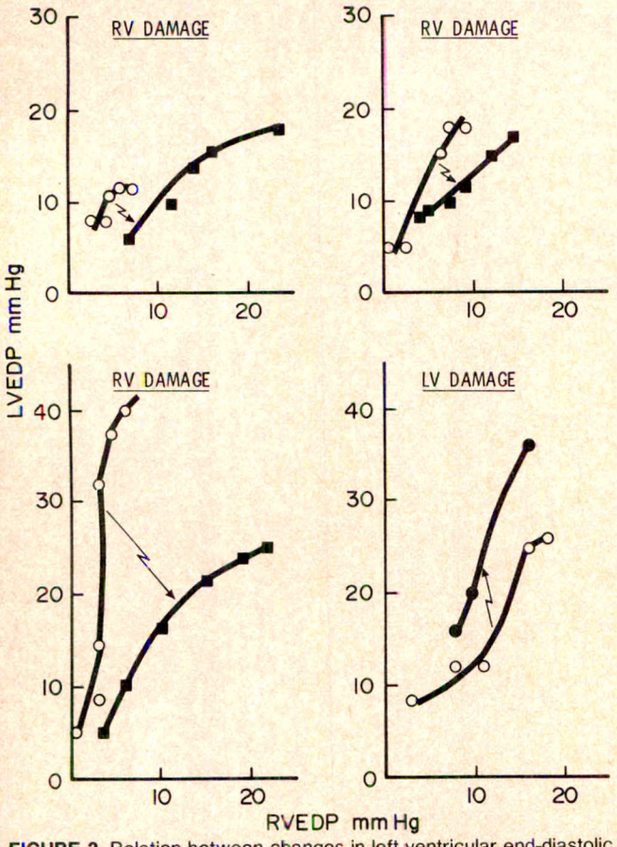

FIGURE 2. Relation between changes in left ventricular end-diastolic pressure (LVEDP) and right ventricular end-diastolic pressure (RVEDP) during volume loading in four dogs. **Open circles** represent measurements in control period before cardiac damage. **Closed squares** (upper panels and lower left panel) represent measurements after right ventricular (RV) cauterization. **Closed circles** (lower right panel) depict pressures during volume loading after left ventricular (LV) cauterization.

sure generated by the right ventricle. Pressure generation averaged 18 mm Hg in the control period and increased to 31 mm Hg during volume expansion. After right ventricular damage, pressure generation was 19 mm Hg, but no significant increase occurred during volume expansion and pressure generation averaged only 20 mm Hg at the end of the infusion period.

Left ventricular damage led to a sharply increased left ventricular end-diastolic pressure and a slightly increased right ventricular end-diastolic pressure. During volume loading, the former pressure increased markedly to an average of 40 mm Hg and surpassed the latter by an average of 25 mm Hg (Fig. 2 and 3).

Aortic Flow

After right ventricular damage, aortic flow was reduced by an average of 20 percent. This reduction in right ventricular output despite a slight increase in right ventricular end-diastolic pressure indicates a considerable shift downward and to the right of the right ventricular function curve (Fig. 4). In contrast, the reduction in left ventricular output was accompanied by a reduction in left ventricular filling pressure consistent with little or no change in left ventricular function. During progressive volume expansion, aortic flow rose to levels more than 50 percent higher than control flow levels but at the expense of a sharp increase in right ventricular end-diastolic pressure and a relatively smaller increase in left ventricular end-diastolic pressure. Therefore, right ventricular damage resulted in a marked shift to the right of the right ventricular function curve so that it then moved to the right of the left ventricular function curve.

Discussion

The right ventricle serves to propel blood through the lungs and to provide an adequate left ventricular filling pressure while maintaining a low central venous pressure. It is therefore the performance of the right ventricle that should account for the fact that left atrial pressure normally is higher than right atrial pressure. The observations of Starr et al.,[1] Bakos[3] and Kagan[4] that damaging the right ventricle did not raise venous pressure requires further scrutiny. If right ventricular function were completely abolished, then left atrial filling might still be maintained if there was an adequate pressure gradient from the right atrium to the left atrium allowing passive flow through a low resistance pulmonary vascular bed. This phenomenon is exemplified in the studies of Rodbard and Wagner,[5] who demonstrated that pulmonary blood flow could be maintained when the right ventricle was excluded from the circulation.

However, right ventricular function persisted in our studies as well as in the catheterization studies of Bakos[3] and Kagan,[4] since the right ventricle generated normal pressures after it had been damaged. The source of systolic pressure in the right ventricle after

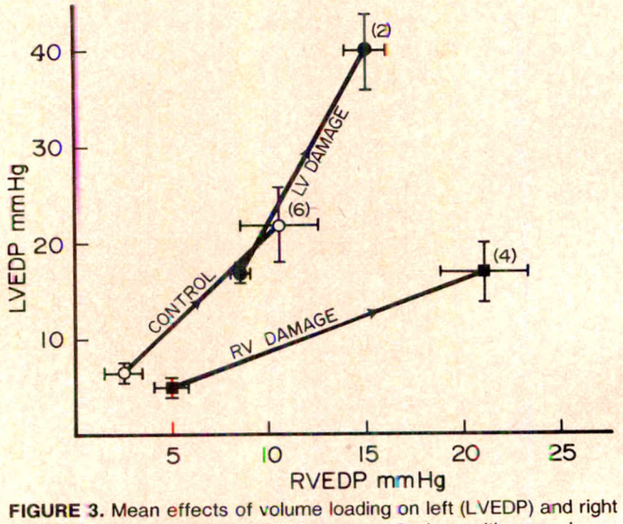

FIGURE 3. Mean effects of volume loading on left (LVEDP) and right (RVEDP) ventricular end-diastolic pressures in dogs with normal ventricles (control) and after right (RV) and left (LV) ventricular damage. **Solid lines** connect values before volume loading with values at the end of volume expansion. **Bars** indicate standard error of the mean. **Numbers in parentheses** indicate number of dogs studied.

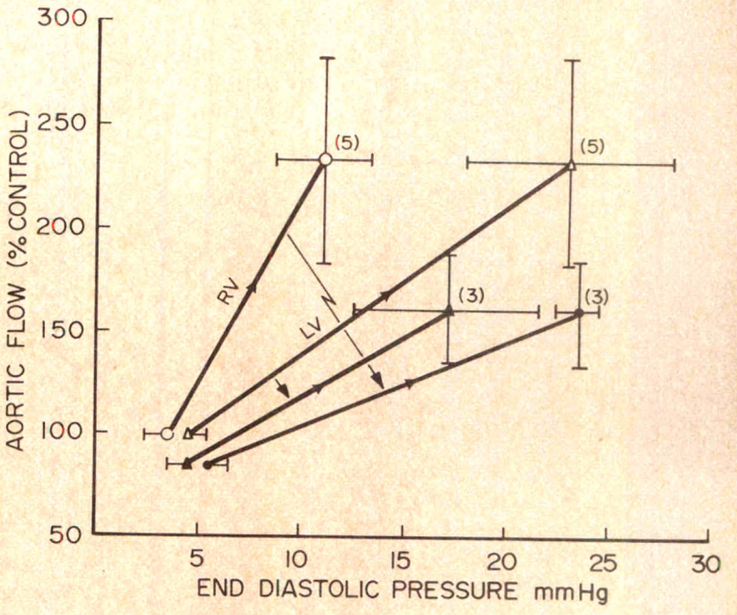

FIGURE 4. Mean relation between aortic flow and left (LV) and right (RV) ventricular end-diastolic pressure during volume expansion before and after right ventricular cauterization. In control period **(open symbols)**, the left ventricular function curve is normally situated to the right of the right ventricular function curve. After cauterization **(closed symbols)** the right ventricular function curve is shifted markedly to the right of the left ventricular function curve. Note that after right ventricular damage, volume flow before volume expansion has been reduced to an average of 70 percent of control flow level. However, flow can still be increased to more than 150 percent of the control level during volume loading.

destruction of this chamber has never been satisfactorily resolved. Since many of the bands of myocardial muscle encircle both ventricles,[6] Bakos[3] suggested that contraction of left ventricular fibers could also generate pressure in the right ventricle. However, the absence of contraction of the free wall of the right ventricle noted both visually and myographically[4] does not support this hypothesis. A more likely explanation is that residual functioning right ventricular fibers, either in the deeper layers of the myocardium less severely damaged by cauterization or in the interventricular septum, are capable of shortening adequately to generate a normal level of resting pressure.[4,7] Since right ventricular contraction involves primarily apex to base shortening rather than a change in transverse diameter, as in the left ventricle,[8] effective pressure generation would not necessarily be abolished by destruction of the right ventricular free wall. Noncompliance of the cauterized portion of the chamber might contribute to the pressure increase when the residual fibers shorten.

Even though the damaged right ventricle exhibited only a slight increase in end-diastolic pressure and was capable of generating a normal systolic pressure, it is clear that right ventricular function was considerably impaired. The pressure gradient between the left and right atria was reduced, and during progressive volume loading a paradoxical right to left ventricular end-diastolic pressure gradient of 1 to 5 mm Hg was maintained. The right ventricular peak pressure generation, which increased during volume expansion in the control period, was unchanged during loading after right ventricular damage. In contrast, left ventricular damage resulted in a disproportionate rise in left ventricular end-diastolic pressure and the gradient between left and right ventricular end-diastolic pressures increased progressively during infusion. It is likely that the increase in right ventricular output that accompanied volume expansion after right ventricular damage was due both to an increase in end-diastolic stretch of the residual functioning fibers and to a passive increase in pulmonary flow resulting from the right atrial–left atrial pressure gradient. Since normal and abnormal cardiac function curves tend to converge at reduced filling pressures,[9] the severity of ventricular dysfunction may become apparent only when the ventricle is challenged with an acute increase in preload. It is also possible that tricuspid regurgitation contributed to the rightward shift of the right ventricular function curve at greater filling pressures.

Clinical implications: The aortic flow measured in these studies is of particular importance in relating these experimental studies to the clinical syndrome of pump failure after myocardial infarction. Although flow was reduced after right ventricular damage it could always be restored to values above control levels by increasing right ventricular end-diastolic pressure. Therefore, low output failure or shock should not complicate this type of experimental right ventricular destruction so long as blood volume is expanded and pulmonary vascular resistance is not increased. The explanation for low cardiac output despite increased right ventricular end-diastolic pressure in patients with right ventricular infarction thus must be attributed to differences in the nature of the damage to the right ventricle or to coexisting left ventricular damage, or both. In contrast to these findings in experimental right ventricular destruction, patients with right ventricular infarction may demonstrate almost complete absence of right ventricular pressure generation. This difference in response probably reflects a difference in the distribution of the myocardial injury, which in patients with ischemic heart disease is likely to involve the septum as well as the free wall and therefore may abolish apex to base shortening. As in clinical acute myocardial infarction,[10] experimental infarction of the left

ventricle resulted in a sharp increase in left ventricular end-diastolic pressure. Support of pulmonary blood flow in this circumstance can be maintained with a near normal right ventricular end-diastolic pressure by virtue of the pumping ability of the right ventricle. When this is impaired by right ventricular myocardial damage, end-diastolic pressure in the right ventricle rises to levels as high or higher than those in the left ventricle and the syndrome of predominant right ventricular dysfunction occurs.

In summary, right ventricular damage produces disproportionate right ventricular dysfunction, but isolated right ventricular damage should not in itself lead to irretrievable circulatory impairment. Nonetheless, right ventricular damage accompanied by left ventricular damage should produce a specific hemodynamic derangement in which predominant right ventricular dysfunction may be accompanied by a low output state. An understanding of the mechanism of the heart failure in this syndrome is a necessary prerequisite to rational management. An increase in cardiac output in this setting probably can be accomplished only if the pressure gradient from the right to the left atrium is increased. This could be accomplished either by volume expansion (Fig. 2) or by a reduction of left atrial pressure.[2]

Acknowledgment

Aldo Notargiacomo and Lee Fong provided valuable technical assistance.

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The Gordon/DonMichael Esophageal Obturator Airway*

A new resuscitation concept, the Esophageal Obturator Airway developed by Dr. Archer S. Gordon and Dr. T. A. Don Michael* offers an effective but simpler method than endotracheal intubation for establishing a patent airway during resuscitation procedures. The Esophageal Obturator Airway is introduced into the esophagus rather than the trachea, and has the following advantages:

- Does not require use of a laryngoscope or other instrumentation.
- Does not require visualization of the larynx or esophagus.
- Does not require any interruption of CPR.

When the airway is inserted and the mask is seated on the face, the obturator tip and inflatable cuff lie in the esophagus below the bifurcation of the trachea. The tip and inflated cuff occlude the esophagus and:

- Prevent gastric distension during resuscitation.
- Prevent regurgitation which leads to aspiration of gastric contents.

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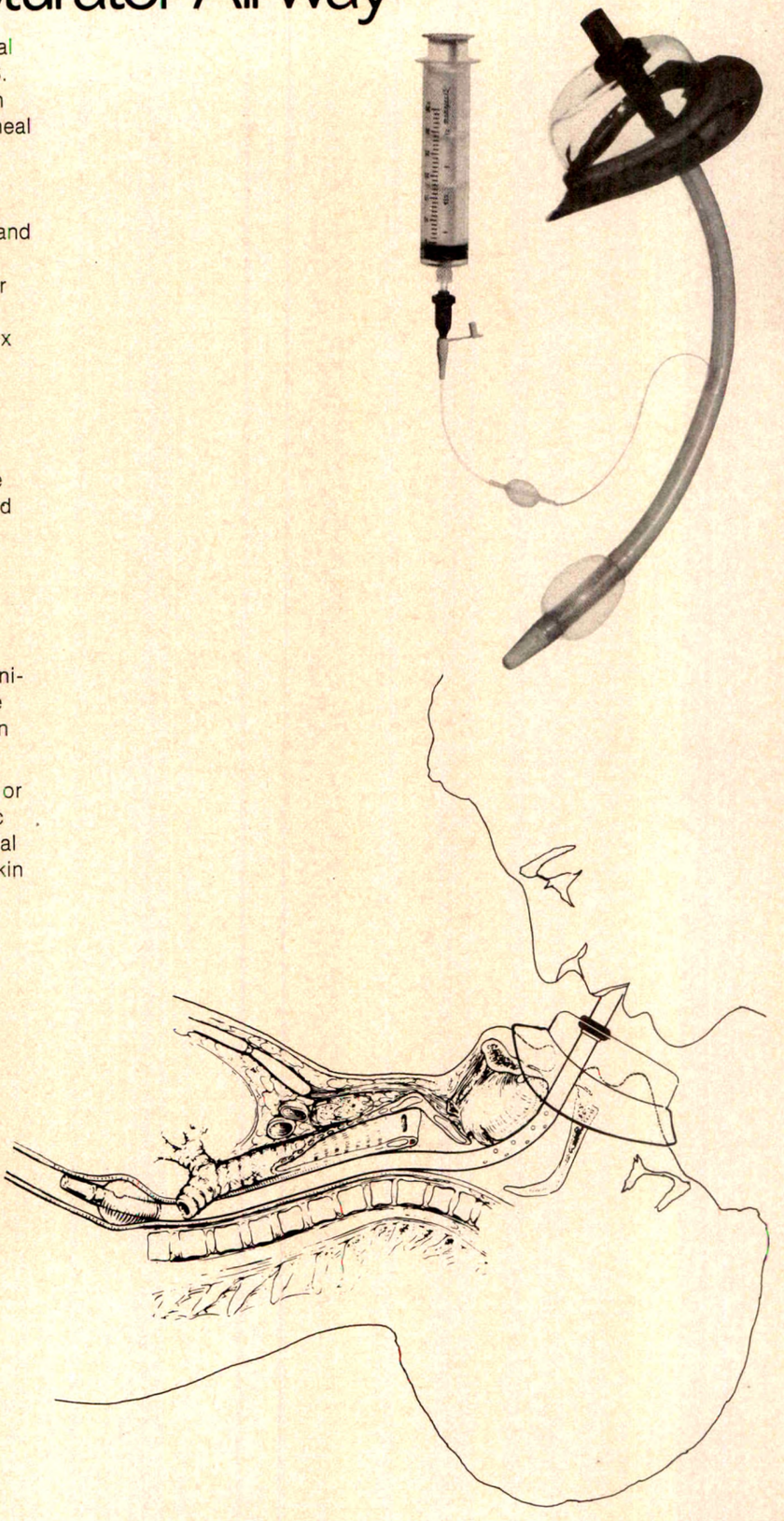

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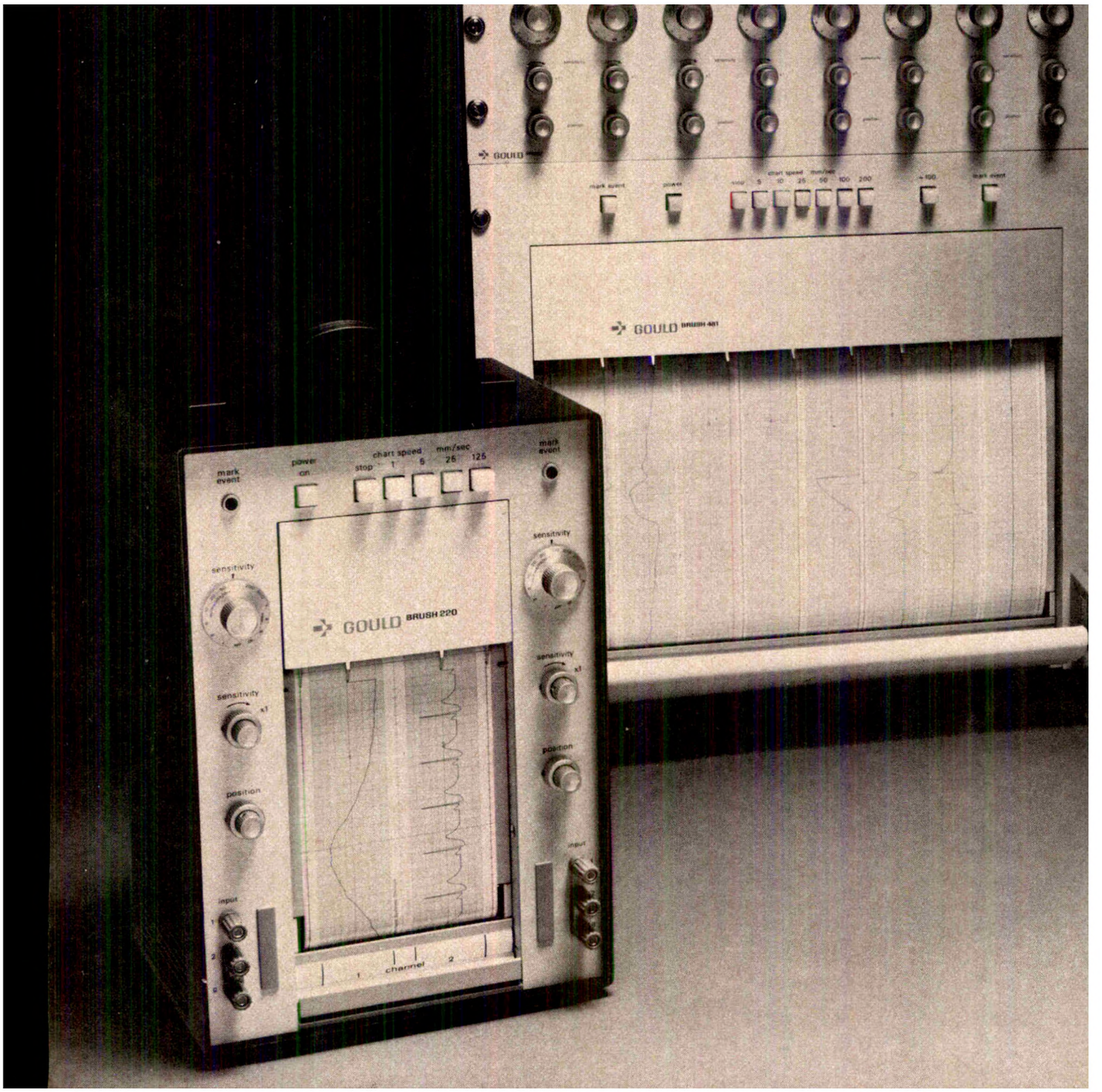
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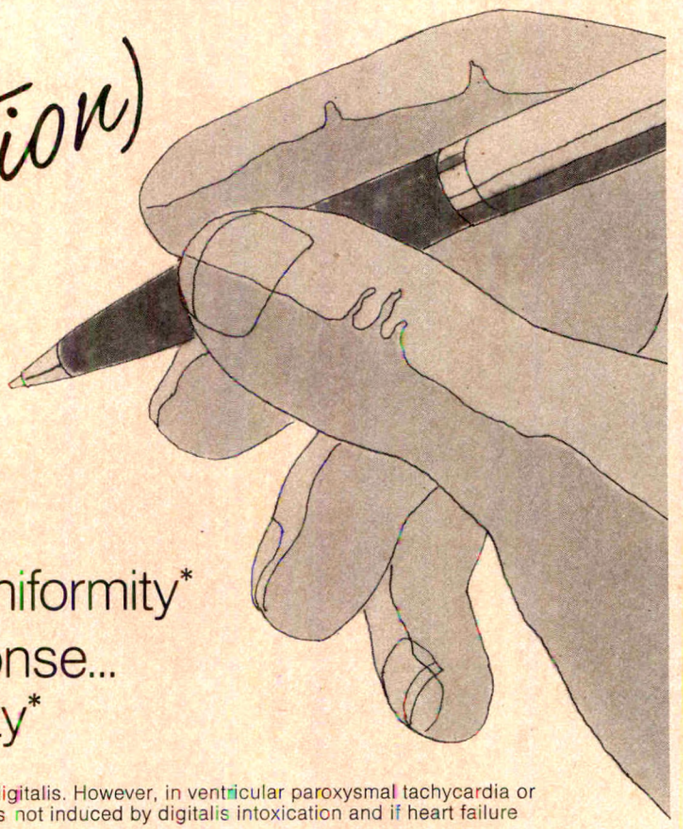

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Complications of Percutaneous Femoral Arterial Catheterization

Prospective Evaluation with the Doppler Ultrasonic Velocity Detector

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Prospective evaluation of vascular complications of 160 percutaneous femoral arterial catheterizations was carried out in 142 adult patients undergoing cardiac catheterization at two affiliated hospitals of the University of Washington. Arterial velocity signals and blood pressure in the limbs were monitored with the Doppler ultrasonic velocity detector before and after each procedure. The rate of complications (14 percent) was similar at each hospital; they included one accidental dissection of the iliac artery and 22 arterial thromboemboli. The location of thromboemboli appeared to be related to the duration of use of an indwelling arterial catheter. Complications were more common in patients, especially female, with mitral valve disease and in patients with coexisting peripheral arterial occlusive disease. Two thirds of the patients with thromboembolic complications had no symptoms. All but one patient with femoral thrombosis had operative thrombectomy; no patient with distal occlusion underwent operation. The Doppler ultrasonic velocity detector is a simple, rapid noninvasive technique for assessing limb hemodynamics in patients undergoing arterial catheterization.

Arterial catheterization has become a valuable technique for diagnosis of cardiac and peripheral vascular diseases, but it continues to have serious consequences for some patients. Although reports indicate that complications after arterial catheterization occur infrequently in experienced centers, several studies suggest that their true incidence may be underestimated. Differences in the reported frequency of catheterization accidents may reflect differences in investigator experience, catheterization methods, patient selection, diagnostic criteria and techniques for detecting complications. The reported rate of such complications increases when the techniques of oscillometry,[1] balloon catheter thrombectomy[2] or withdrawal angiography[3] are routinely used after catheterization.

To evaluate the efficacy of improved catheterization techniques, material modifications or pharmacologic prophylaxis in preventing catheterization accidents, accurate methods for diagnosing these complications must be developed. Because the results of pulse detection by different observers are variable, this method of assessing arterial circulation is an unreliable guide to the presence of occlusion after catheterization. The recent development of the Doppler ultrasonic velocity detector and methods for measuring segmental limb blood pressures have permitted accurate, objective noninvasive assessment of circulatory hemodynamics in peripheral arterial disease.[4] Our investigation therefore used these techniques to assess prospectively complications of cardiac catheterization by the percutaneous femoral arterial route.

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TABLE I

Vascular Complications of Femoral Arterial Catheterization

Hospital	Catheterizations (no.)	Complications	
		no.	%
University Hospital	99	15	15
Veterans Administration Hospital	61	8	13
Total	160	23	14

Methods and Materials

From June 1 through December 31, 1971, a total of 142 adult patients undergoing cardiac catheterization by percutaneous femoral arterial cannulation were studied at the University Hospital and the Veterans Administration Hospital of the University of Washington. The Seldinger technique of femoral arterial catheterization was similar at the two hospitals. Catheters were wiped and frequently flushed with heparinized saline solution. Systemic heparinization was not used. Coronary arteriography by the femoral route was performed by the Judkins technique.

Patient assessment before and after catheterization included recording of peripheral pulses, arm and ankle systolic pressures detected by Doppler ultrasound[5] and evaluation of the quality of arterial signals[6] by the ultrasonic velocity detector (Parks Electronics Laboratory, Beaverton, Ore.). For measurement of systolic blood pressure, pneumatic cuffs with 8 by 40 cm inflatable bladders (Statham Instruments, Oxnard, Calif.) to encircle the limb completely were placed on an arm and both ankles. With the ultrasonic probe positioned over a distal limb artery (radial, posterior tibial or dorsalis pedis) the corresponding limb cuff was inflated so that cuff pressure exceeded the patient's systolic pressure, thus obliterating the Doppler arterial signal. The cuff was then slowly deflated until the level of systolic pressure was reached at the point of return of an audible Doppler arterial velocity signal. The values for systolic pressure measured by the Doppler technique correspond closely with direct intraarterial pressure measurements (reported correlation coefficient 0.991).[7]

Systolic blood pressure in the ankle, as determined by ultrasound, is normally equal to or greater than that of the arm.[4] Criteria for thromboembolic complications in our study were systolic pressure in the ankle more than 20 mm Hg less than that in the arm and abnormalities of the arterial velocity signals. The normal arterial velocity signal is multiphasic, with a prominent systolic component and one or more distinct diastolic components. Distal to an obstruction the arterial velocity signal may become attenuated, with loss of the separate diastolic sound components. A loss of peripheral pulses usually coexists, but this sign was not used as a sole criterion of arterial complication because of the recognized variability of pulse detection by different observers.

Patients with coexisting peripheral arterial occlusive disease demonstrated before catheterization both a lower level of systolic pressure in the ankle than in the arms and abnormalities in the arterial velocity signal distal to the obstruction. Thromboembolic complications after catheterization in these patients were manifested by a further reduction in ankle systolic pressure in relation to pressure in the arm.

The anatomic location of the arterial occlusion was defined by segmental limb blood pressures measured at the proximal thigh, above and below knee and ankle levels.[8] A pressure gradient greater than the normal 20 to 30 mm Hg between two adjacent levels of measurement indicated arterial obstruction between those sites. The level of abnormal arterial signals detected with the ultrasonic velocity detector was a further indication of the site of thromboembolic occlusion. Arteriographic studies to identify thromboembolic occlusion were not performed.

TABLE II

Site of Arterial Complications

Hospital	Iliac Dissection	Thromboemboli	
		Femoral	Below-Knee
University Hospital	1	7	7
Veterans Administration Hospital	0	0	8

Results

There were 92 male and 50 female patients aged 14 to 77 years (mean age 48 ± 10 [1 standard deviation]). They underwent a total of 160 percutaneous femoral arterial catheterizations, 99 performed at the University Hospital and 61 at the Veterans Administration Hospital. The prevalence of arterial complications after catheterization (14 percent) was similar at each hospital (Table I). Three deaths occurred, all secondary to myocardial infarction associated with the procedure.

Except for a single instance of dissection of the iliac artery by a catheter, the arterial complications in this study were thromboembolic (Table II). There was no instance of major hemorrhage, false aneurysm or arteriovenous fistula. The pattern of location of the arterial occlusion differed at the two hospitals. At the University Hospital half of the thromboemboli involved the femoral artery and half occurred below the knee; at the Veterans Administration Hospital all arterial occlusions were distal to the femoral artery. These differences may be related to the mean duration of use of an indwelling arterial catheter at each institution. At the University Hospital, where about half of the procedures are performed for valvular heart disease, the mean duration of use of an indwelling arterial catheter (53 ± 23 minutes) was significantly longer ($P < 0.001$) than at the Veterans Administration Hospital (35 ± 22 minutes) where more than three quarters of the studies involved selective coronary arterial catheterization. The mean duration of use of an indwelling arterial catheter in patients with femoral thromboemboli (53 ± 22 minutes), was

significantly longer than the duration in patients with distal occlusions (34 ± 20 minutes) (P <0.001). There was no significant difference between the duration of use of an indwelling catheter in patients with thromboemboli and in those with no complications.

The frequency of complications did not correlate significantly with age, body surface area or cardiac index. However, patients with mitral valve disease (stenosis, regurgitation or combined lesions) had a significantly higher rate of complications (32 percent, Table III) than patients with other forms of cardiac disease (12 percent) (P <0.01). The significantly greater frequency of complications in female than in male patients (P <0.05) may be explained by the fact that mitral valve disease appeared predominantly in the former. An attempt to assess the factor of sex in each diagnostic group revealed no statistically significant differences, perhaps because of insufficient numbers in each sample.

Precatheterization screening studies with the Doppler ultrasonic velocity detector revealed 18 patients (13 percent of all patients studied) with coexisting peripheral arterial occlusive disease in one or both legs. Eleven limbs with diseased vessels were catheterized, and complications occurred in 8, representing 33 percent of all complications in our study. Each hospital demonstrated this high risk of vascular accidents after catheterization of atherosclerotic arteries.

Symptoms: Only one third of the patients with thromboembolic complications had symptoms of ischemia such as pain, subjective coldness, paresthesia or muscle weakness (Table IV). This low frequency of symptoms occurred in patients with femoral arterial occlusion as well as those with distal thromboemboli. Although peripheral pulse deficits were documented by at least one observer in all but one of these patients, there was considerable variability in the pulses recorded by different observers. Pulse detection was thus not considered a reliable guide to the presence or location of thromboembolic complications in our study.

Treatment and results: Operative thrombectomy with successful restoration of circulation was carried out in all but one of the patients with femoral arterial occlusion. In all patients operated on, fresh clot was retrieved from the femoral artery. There was no instance of intimal flap or other vascular injury associated with the obstruction. The single patient with femoral arterial occlusion who did not undergo operation never had significant ischemia and had excellent collateral circulation as evaluated with the ultrasonic velocity detector. Patients with distal thromboemboli did not undergo operation, and all but one had excellent recovery of distal perfusion by collateral circulation or spontaneous lysis of the occlusions. One patient with preexisting peripheral arterial occlusive disease had significant ischemia after occlusion of the single remaining patent below-the-knee vessel of the catheterized limb. Although this patient's leg remained viable, he succumbed to severe generalized coronary artery disease 6 weeks after catheterization. None of the remaining patients with arterial complications died during the study.

TABLE III

Prevalence of Arterial Complications in Patients With and Without Mitral Valve Disease

Arterial Complication	Mitral Valve Disease		Other Disease	
	Male	Female	Male	Female
None	9	12	72	26
Present	2	8	9	4
Total	11	20	81	30

Discussion

Although the information afforded by cardiac catheterization more than justifies its inherent risks, efforts to reduce these risks deserve continued attention. The prevalence of arterial vascular accidents after catheterization is generally reported to be less than 5 percent.[9–11] However, most studies are retrospective and document only more serious symptomatic complications. Thromboembolic accidents are usually detected only by the presence of pulse deficits. The recognized fallibility of pulse detection by various observers, again demonstrated in our study, makes palpability of pulses an unreliable criterion for assessment of peripheral circulation. Because thromboembolic complications are frequently asymptomatic—as in two thirds of our patients—it is important to develop more objective techniques for assessing the peripheral circulation in patients undergoing cardiac catheterization.

Several investigators have documented an increased frequency of observed complications after arterial catheterization when more sensitive criteria are utilized for diagnostic assessment. Jacobsson et al.[1] noted a greater accuracy in detecting thromboembolic complications when oscillometry was routinely used before and after catheterization. Although many of their patients with detected abnormalities had minimal symptoms and often had pulses, thromboemboli were always retrieved at operative exploration. Formanek et al.[3] described frequent detection

TABLE IV

Symptomatic Thromboemboli

Site of Occlusion	Patients with Thromboemboli	
	Total no.	no. with Symptoms
Femoral artery	7	2
Below-knee artery	15	5
Total	22	7

of thrombotic material on arterial catheters when withdrawal angiography was employed. Local or distal embolization of such thrombotic material after catheter removal was likewise demonstrated arteriographically. Baker et al.[2] documented retrieval of thrombus in more than 50 percent of patients subjected to routine balloon catheter embolectomy at the time of brachial arterial catheterization. These experiences have led to efforts to minimize such complications by improving techniques, catheter materials and pharmacologic prophylaxis. However, these measures can be properly evaluated only if the existence of thromboembolic accidents can be defined accurately and objectively.

The Doppler ultrasonic velocity detector has been of established utility in the physiologic assessment of patients with peripheral arterial occlusive disease. Because its use is simple, rapid and noninvasive, this instrument lends itself well to screening and follow-up studies of the peripheral circulation. The characteristic multiphasic pattern of the normal arterial velocity signal is lost distal to an arterial occlusion, thus permitting localization of an obstructive process. The determination of arm, ankle and segmental limb pressures permits a fairly reliable quantitative estimate of the severity of the arterial occlusion.

Our study documents the relatively greater frequency of arterial thromboembolic accidents after catheterization when a sensitive objective technique is used for diagnosis. The prevalence of complications was similar at the two hospitals, but the distribution of thromboembolic occlusions differed. The lack of more proximal, and presumably larger, emboli at the Veterans Administration Hospital may have been related to the shorter average period of use of an indwelling arterial catheter at that hospital. Other factors, such as the type of catheter used and the patients' sex (all but two patients at the Veterans Administration Hospital were male) may have been contributory. Despite the differences in duration of the catheterization procedure at the two hospitals, there were no differences in the period of use of an indwelling catheter in patients with and without complications at either institution.

The significantly greater frequency of complications in female patients and in patients with mitral valve disease has been noted by other investigators.[12] There were too few patients in our study to permit statistical analysis of the independent contribution of these variables.

Prevention: Routine assessment of the peripheral circulation of patients before catheterization revealed a significant number of patients (13 percent) with coexisting peripheral arterial occlusive disease. Many of these patients had no prior history of claudication, although their underlying cardiac disease may have restricted their activity sufficiently to mask symptoms of arteriosclerosis obliterans. The importance of recognizing peripheral arterial disease is reflected in the high frequency of complications (73 percent) in patients catheterized by way of an atherosclerotic artery.

If preexisting arterial occlusive disease is discovered in a limb with the ultrasonic velocity detector, every effort should be made to use another limb as a route for arterial catheterization. This dictum is important regardless of the location of disease in the affected limb. Proximal obstructions may cause difficulty in catheter passage and increase the risk of arterial dissection or thrombotic occlusion. Distal disease limits arterial runoff, making the limb more susceptible to ischemia after the occurrence of distal thromboemboli that might be well tolerated in the normal limb. This phenomenon was manifested by the patient in this series who had severe ischemia after distal embolic occlusion of the left anterior tibial artery, his only patent vessel below-the-knee before catheterization. In limbs with preexisting arterial disease, thrombectomy may be difficult or even unsuccessful unless more extensive reconstructive techniques are used.

Diagnosis of thromboembolic complications: Our data indicate that as many as two thirds of patients with thromboembolic complications after catheterization may be asymptomatic, whether they have occlusion of the femoral artery or distal obstruction. The maintenance of limb blood flow through collateral circulation accounts for the lack of symptoms, especially in patients at bed rest after the catheterization procedure. Such patients have no symptoms until their activity increases upon discharge from the hospital. With development of adequate collateral circulation or dissolution of thromboemboli, symptoms may never develop. Measurement of the resting ankle blood pressure with the Doppler ultrasonic velocity detector provides a reliable guide to the adequacy of peripheral circulation. Furthermore, the level of ankle systolic blood pressure correlates well with limb blood flow during exercise and the period of postexercise reactive hyperemia.[13] This physiologic information may be a valuable guide to management of patients with thromboembolic complications after catheterization.

Operative thrombectomy: In our study all but one patient with occlusion of the femoral artery underwent operative thrombectomy with successful restoration of circulation. Although all but two patients were asymptomatic, operative management seemed indicated because of the possibility of future claudication and the fact that removal of thrombus from a major vessel can be simply performed with a great chance of success. One patient with a femoral arterial thrombus had excellent collateral circulation and operation was not performed in light of his severe cardiac disease.

No patient with thromboembolic occlusion of arteries below the knee underwent operation. Except for the aforementioned patient with coexisting severe arteriosclerosis obliterans, no patient had significant ischemia and all had excellent peripheral circulation as determined with the ultrasonic velocity detector. Since distal emboli may be difficult to remove with the balloon catheter and complications may occur with repeated attempts at thrombectomy, operation

may be justifiably avoided in such patients when adequate distal perfusion can be objectively established.

Clinical implications: The results of our study suggest the value of objective physiologic monitoring of the peripheral circulation in patients undergoing arterial catheterization. This principle can be applied not only to percutaneous femoral arterial catheterization but also to translumbar angiography and brachial arterial cutdown techniques.[14] The Doppler ultrasonic velocity detector is a simple noninvasive instrument and is well accepted by patients. The quality of arterial velocity signals and the segmental measurement of limb blood pressure may be readily determined. These hemodynamic evaluations permit rapid screening for preexisting vascular disease, monitoring for thromboembolic complications and physiologic guidance in the management of such catheterization accidents. Finally, the ability to assess more accurately the status of the peripheral circulation will enhance future evaluation of various prophylactic measures to reduce the frequency of complications of cardiac catheterization.

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New Instrument for Transvenous Cardiac Biopsy

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A new forceps is described for obtaining serial endomyocardial biopsy specimens from the human heart. The instrument is introduced percutaneously into the right internal jugular vein and used to obtain tissue from the apex of the right ventricle. Eighty-five biopsy procedures have been performed in 19 patients after cardiac transplantation. The technique used was 100 percent successful in obtaining endomyocardial biopsy specimens, and there were no significant complications. A biopsy procedure may be performed within 5 minutes. Serial percutaneous transvenous endomyocardial biopsies are now routinely performed with this instrument in new heart transplant recipients and in patients with primary cardiomyopathy.

Although biopsy of the kidney, liver and many other organs is routine in clinical medicine, biopsy of the heart is infrequently performed. Consequently, knowledge is limited about serial histologic changes that occur in myocardial disease. Reported techniques for obtaining myocardial biopsy specimens have included percutaneous needle biopsy of the left ventricle,[1] catheter needle biopsy of the interventricular septum[2] and open thoracotomy.[3] The morbidity and mortality associated with these methods have precluded their widespread acceptance.

Transvenous biopsy of the endomyocardium of the right or left ventricle was first described 11 years ago by Sakakibara and Konno.[4] However, despite the availability of the Konno-Sakakibara bioptome in this country, there have been few reports[5,6] of its use outside Japan. The potential value of serial biopsy of the orthotopically transplanted canine heart in the diagnosis of acute cardiac allograft rejection encouraged us to develop a technique in our laboratory[7] for repeated cardiac biopsy in the dog by way of the external jugular vein. Subsequently, development of a technique[8] for percutaneous introduction of the biopsy forceps into the internal jugular vein in man provided a means for obtaining serial endomyocardial biopsy specimens from the human heart.

Our initial clinical experience[9] with cardiac biopsy using the Konno-Sakakibara bioptome was unsatisfactory. This instrument has many small moving parts, and the poor mechanical advantage of the jaws results in frequent failure to remove a satisfactory specimen from the right ventricular endocardial surface. We therefore designed the new cardiac biopsy forceps described in this report. Using this instrument, we have now performed 85 cardiac biopsy procedures with uniform success and without significant complication in 19 patients after cardiac transplantation.

The Instrument

The cardiac biopsy forceps is an integral unit with three main parts (Fig. 1A). The handle is similar to that on most surgical instruments and includes a ratchet so that the jaws may be locked. A flexible spiral wire catheter cov-

From the Division of Cardiovascular Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, Calif. This work was supported by U. S. Public Health Service Grants HL 08696-09 and HL 13108-04, and Grant RR-70 from the General Clinical Research Centers, Division of Research Resources. Manuscript accepted July 11, 1973.

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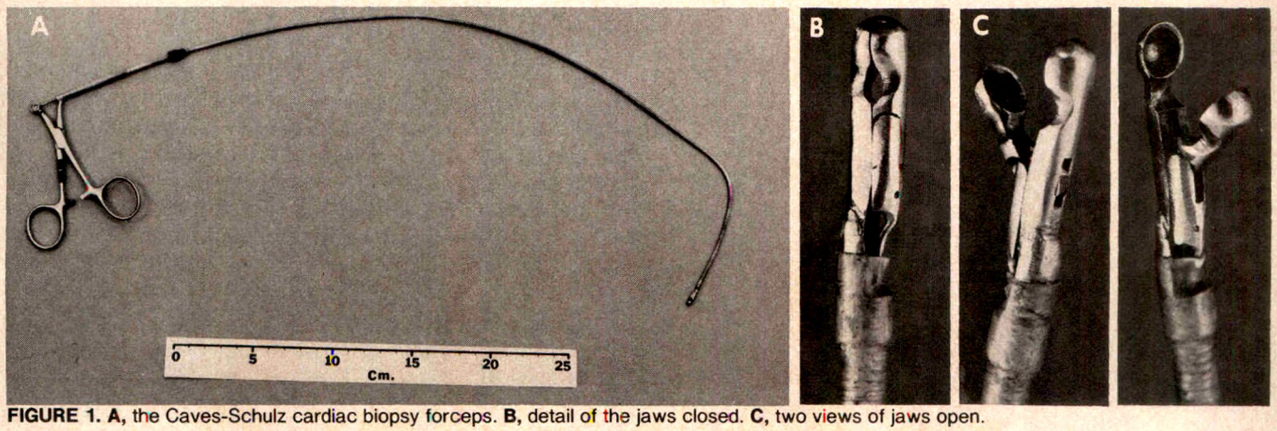

FIGURE 1. A, the Caves-Schulz cardiac biopsy forceps. **B,** detail of the jaws closed. **C,** two views of jaws open.

ered with Kynar® shrink tubing is attached to one end of the handle, and a stiff, flexible wire that passes through the catheter is attached to the other end. Opening and closing the handle controls the jaws, which are welded to the other ends of the catheter and wire. The jaws consist of one fixed and one mobile part, each ending in a hollow cup 1.5 mm in diameter. The edges of the cups are sufficiently sharp to permit removal of the specimen by a cutting action rather than avulsion. When the jaws are closed and locked, the instrument has a smooth rounded tip that passes through a no. 9F catheter sheath (Fig. 1B); when they are open, the jaws have a span of 2.5 mm (Fig. 1C). The catheter is 50 cm long. Sliding on the catheter is a rubber plug that fits into the Luerlok connection on the sheath and prevents escape of blood around the catheter. In addition, Teflon® seals are present at both ends of the catheter to prevent penetration of blood beneath the catheter tubing.

Immediately before use, the biopsy catheter is bent at a right angle 7 cm from the tip (Fig. 1A). This bend is then stiffened by brief immersion in ice-cold saline solution. After the catheter is inserted through the sheath, the right angle of the bend is reduced to approximately 30°, which is usually ideal for passage of the catheter through the tricuspid valve.

Biopsy Technique

There has been little change in our biopsy technique described for use with the Konno-Sakakibara bioptome.[8] Under local anesthesia, a no. 16 Medicut cannula is inserted directly into the right internal jugular vein. A flexible guide wire is then inserted through the cannula and a no. 9F Desilets-Hoffman false catheter and sheath are passed over the guide wire into the vein. The biopsy forceps are introduced through the sheath and the rubber plug is inserted into the Luerlok connection of the sheath to prevent leakage of blood. The forceps are then advanced to the apex of the right ventricle under fluoroscopic control (Fig. 2). The open jaws of the instrument can easily be pressed against the endocardium from this approach, since the catheter has only a gentle curve in the region of the tricuspid valve. The jaws are then closed and the instrument is withdrawn steadily. A jerk occurs as the specimen is removed from the endomyocardium. After retrieval of the biopsy specimen from the jaws of the forceps, the instrument may be reintroduced to obtain additional specimens. Finally, the sheath is removed from the vein, and pressure is applied over the puncture site with the patient sitting up-

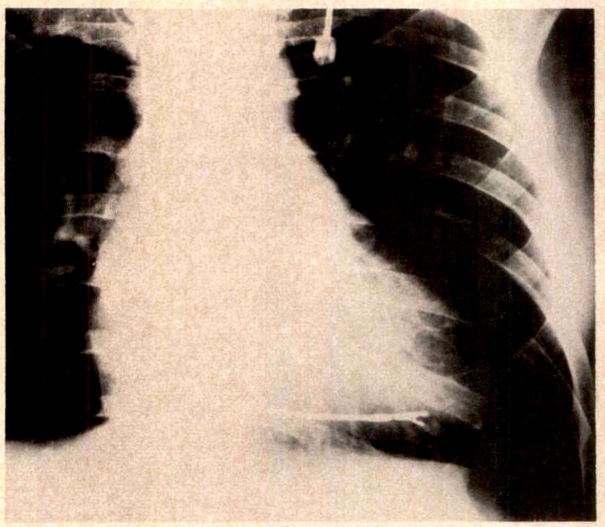

FIGURE 2. Plain chest X-ray film showing the biopsy forceps in the right ventricle.

right. Bleeding is immediately controlled and the vein remains patent for subsequent use.

The biopsy procedure can usually be completed within 5 minutes and requires less than 1 minute of fluoroscopy. The electrocardiogram is monitored throughout the procedure, and a chest X-ray film is obtained afterward.

Results

One hundred and sixty-three biopsy specimens have been obtained from 19 transplanted human hearts during 85 biopsy procedures (Table I). On most occasions two specimens were removed, but in some cases as many as four separate specimens were obtained by repeated introduction of the catheter. The majority of biopsies were performed in transplant recipients during the early postoperative period, and were utilized for direct histologic assessment of acute graft rejection (Fig. 3) and the response to immunosuppressive treatment.[10] In eight long-term survivors biopsy specimens were obtained either dur-

TABLE I
Cardiac Biopsies Performed in 19 Patients

Case no.	Biopsy Procedures (no.)	Biopsy Specimens (no.)	Indications for Biopsy	Complications
1	8	16	Early postoperative management	None
2	2	4	Early postoperative management	None
3	8	15	Early postoperative management	None
4	9	18	Early postoperative management	None
5	8	14	Early postoperative management	None
6	7	10	Early postoperative management	Pneumothorax
7	7	14	Early postoperative management	None
8	8	14	Early postoperative management	None
9	2	4	Early postoperative management	None
10	10	19	Early postoperative management	Atrial fibrillation
11	3	4	Early postoperative management	None
12	1	1	Late acute rejection	None
13	3	7	Late acute rejection	None
14	2	4	Late acute rejection	None
15	2	6	Late acute rejection	None
16	2	4	Long-term survivor (evaluation)	None
17	1	3	Long-term survivor (evaluation)	None
18	1	2	Long-term survivor (evaluation)	None
19	1	4	Long-term survivor (evaluation)	None
Totals	85	163		2

ing episodes of suspected late acute rejection or during routine late postoperative evaluation.

We have never failed to obtain tissue during a biopsy procedure with the new forceps described in this report. Minor complications were encountered in two patients, but they could not be related directly to the use of the forceps. In one patient a small pneumothorax was produced during introduction of the Medicut cannula. In another patient, who had previously had repeated episodes of atrial fibrillation, the arrhythmia recurred during performance of the biopsy procedure.

Discussion

Serial cardiac biopsy may offer new insight into the pathogenesis and clinical management of cardiac disease. The transplanted heart is perhaps uniquely accessible to this technique since striking and readily observed changes in endomyocardial histologic features evolve rapidly during acute episodes of graft rejection. Thus, the value of serial cardiac biopsy with the new instrument described here was readily demonstrated in our population of transplant recipients.

Features we considered essential in the design of our biopsy forceps and its use in patients receiving immunosuppression therapy were safety, efficiency and patient acceptance. Our experience to date has confirmed that these criteria have been satisfied, and frequent cardiac biopsy is now a routine aspect of clinical management during the first 2 months after transplantation. Percutaneous insertion of the forceps under local anesthesia into the right internal jugular vein provides rapid and direct access to the region of the right ventricle. The stiffness of the catheter and wire permits controlled manipulation and firm application of the jaws to the endocardial surface. The strength and cutting action of the jaws result in easy removal of the specimen, whose size is

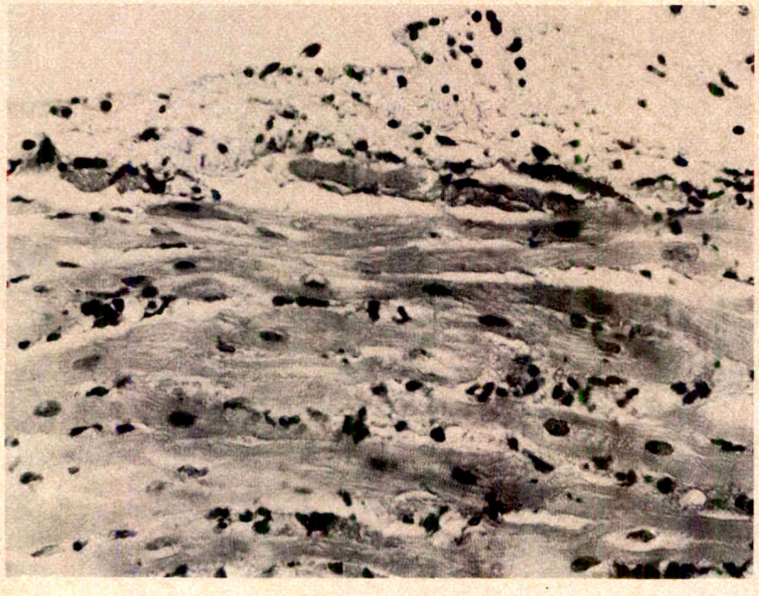

FIGURE 3. Biopsy specimen from a cardiac transplant recipient. The histologic detail is excellent and shows severe acute cardiac allograft rejection with edema of the endocardium and myocardium, lymphocytic cell infiltration and fibrinous exudate. (Hematoxylin-eosin ×320, reduced by 25 percent.)

limited by the dimensions of the jaws. Multiple specimens can be obtained by repeated introduction of the forceps through the indwelling catheter sheath in the internal jugular vein. After removal of the sheath, the vein remains patent and available for subsequent cannulation, and the skin puncture site heals to an imperceptible scar without suturing. The entire procedure can be completed within several minutes.

Our experience with 163 biopsies during 85 procedures without significant complications testifies to the safety of our biopsy technique. The risk of this procedure is similar to that of right heart catheterization by way of a central vein, and thus would appear to be substantially less than that associated with left ventricular needle biopsy by percutaneous puncture (hemorrhage, cardiac tamponade, ventricular fibrillation).[1] The technical difficulties encountered in transvenous biopsy by way of peripheral veins, as previously described,[5,6] are avoided. On the basis of our favorable experience with cardiac transplant recipients, we have extended this technique to the study of patients with primary myocardial disorders.

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Julius Cohnheim's Experiments on Heart Valves

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Surgical operations on the valves of the human heart have attracted the attention and aroused the admiration of many persons who are not directly concerned with surgery or even with any branch of medicine. Not long ago these procedures were a spectacular rarity. If nowadays they are no longer rare, they have nevertheless not ceased to excite wonder.

It has been difficult to determine exactly and reliably who first performed these operations. The trail obviously leads back to the European experimental physiologists of the second half of the 19th century. A previous article in the present historical series contained excerpts from one of the earliest contributions, an essay by Edwin Klebs (1834–1913), "On Operative Wounds of the Heart Valves and Their Consequences." This appeared originally in the *Prager Medicinische Wochenschrift*, volume 1, pages 29–36, 1876.[1] Not long after, Ottomar Rosenbach (1851–1907) issued a thesis, "Ueber artificielle Herzklappenfehler, Eine experimentellpathologische Abhandlung" (On Artificial Insufficiency of the Heart Valves, a Treatise on Experimental Pathology, Breslau, 1878, 39 pages[2,3]).

Rosenbach was a pupil of Julius Cohnheim (1839–1884), one of the great geniuses of experimental pathology.* Cohnheim's statement, which follows, indicates that his experiments preceded those of Rosenbach. The excerpts from Cohnheim have been taken, with slight modification, from his Lectures on General Pathology,[5] translated from the second German edition by Alexander B. McKee.[5] The original appeared in 1877 to 1880.

Excerpts from Cohnheim

. . . Now, should one of the morbid conditions just described be established in connection with the heart, it follows as a direct conclusion from our recent discussions that the work done by the organ must be augmented to correspond with the increased demands upon it; and this will occur whether the entire heart or only single parts are concerned. At any rate this is the result to which we have been led by our reflections. But in order to determine whether this increase really takes place, we shall again have recourse to the experimental method. If one of the lesions described above be produced artificially in a healthy animal, a simultaneous examination of the arterial and venous circulation, on the one hand, and of the intracardiac pressure, on the other, must afford reliable information on the point at issue. With this object a very simple, but it is true imperfect, method of demonstration may be resorted to. Nothing more is necessary than the production of artifical aortic insufficiency by perforating the aortic valves of an animal.† The experiment can almost always be carried out successfully in the rabbit, and with still greater certainty in the dog. A thin metallic sound, furnished at its distal end with a button, is introduced into the carotid in the direction of the heart, and if carefully manipulated, may quite easily be made to perforate at least one, sometimes two, or perhaps all three segments; or one may even succeed in partially tearing them from their attachment to the aorta. That laceration of the valves has been successfully effected is not merely apparent to the operator as he guides the instrument; as a rule, a loud, mostly whistling murmur, audible over the base of the heart, at once affords proof of positive success. Most unmistakable information is, however, derived from the arterial pressure-curve, where the peculiar characters of the pulse of aortic insufficiency, shortly to be discussed, immediately make their appearance. But although there is no doubt that the aortic valves are perforated, and no longer able to effect complete closure of the orifice during the ventricular diastole, *the mean arterial pressure continues at precisely its former level*, nor is the venous pressure in the least influenced by the operation. This result, while making it extremely probable that the work done by the left ventricle has increased in consequence of the insufficiency, does not, however, directly prove it. There is, moreover, in the experiment the inherent drawback that the amount of insufficiency is not under control, since the number of segments perforated and the size of the perforations are more or less matters of chance, and there is no possibility of determining the extent of the injury *intra vitam*. Much more instructive therefore, although more complicated, is another experimental procedure, by which *stenosis*, and not insufficiency, of the arterial ostia is produced artificially.

This experiment, like that on positive pericardial tension, is carried out on a curarized dog, whose respiration is maintained artificially, the first step being the formation of a large window in the left half of the thorax by an ample re-

This study was based on research assisted by the National Institutes of Health (Grant HL-10948).

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* Cohnheim laid the basis for our knowledge of the mechanism of inflammation. I have discussed his contributions to this subject in previous issues.[4]

† This experiment was first communicated in the first edition of these lectures, vol. i, p. 38; described more in detail, as well as supplemented and developed especially in the clinical direction, by Rosenbach in his inaugural thesis, 'Ueber artificielle Herzfehler,' Breslau, 1878, and 'Arch. f. experiment. Path.,' ix, p. 1; since wrongfully called in question by J. Goddard, 'Kunstmatig opgewekte gebreken van het ostium aortae,' J. D. Leiden, 1879.

section of the ribs. The pericardium is then opened at its upper end, in the neighborhood of its reflection, and the cellular and adipose tissues binding together the aorta and pulmonary artery immediately above their origins are divided by means of two pairs of forceps. The greatest caution must be exercised here, since the thin-walled pulmonary artery is extremely susceptible of injury. A strong thread is then passed round the artery of which it is desired to produce stenosis, and the ligature is secured in a loop-knot, such as is employed in surgery under the name of "Graefean." The lumen of the aorta or of the pulmonary artery can now be more or less constricted at discretion by means of the ligature. The curve of the *arteria femoralis* (this vessel being connected with the kymograph) and a soda-manometer in connection with the *vena jugul. sin.* simultaneously supply us with information as to the pressure relations in the systemic vessels. The intracardiac pressure is registered by one of the manometers of the kymograph, connected with a comparatively wide glass tube introduced into the corresponding ventricle. The glass tubes employed for this purpose are closed at the cardiac end and provided with a lateral aperture; they should be filled with a 0.6 per cent solution of common salt and introduced into the heart; the introduction being carried out, on the right side, from the *v. jugul. ext. dextra,* and on the left, from left auricular appendage, which is then secured by a ligature round the tube. The tube may be most conveniently connected with the manometer of the kymograph, after the method of Goltz and Gaule,* by means of another forked one, the two limbs of which serve as manometers. One limb is provided with a valve allowing the ascent, but not the descent, of the column of mercury, and acts as a maximum manometer, while the other forms a manometer of the ordinary kind.

The animal being thus prepared, let us begin with the production of *stenosis of the pulmonary artery,* regulating its severity by the amount of twist communicated to the ligature-rod. Now, you may increase the twist either slowly and gradually but continuously, or intermittently, and carry it to such a pitch that a very marked constriction of the pulmonary artery becomes apparent not only to the examining finger, but to the naked eye—for all that, *you cannot detect the slightest change in the femoral curve or in the manometer in the jugular;* mean pressure, pulse, and respiratory undulations, everything remains exactly as before. A change occurs only when the stenosis is carried beyond a certain point. *The arterial pressure then undergoes a steep and sudden descent,* while at the same time the level of the venous manometer rapidly rises; the femoral curve approaches to within 10–15 mm. of the abscissa, the respiratory undulations cease, the pulsations become extremely small, their rhythm considerably retarded and quite irregular; and, if the ligature is not loosened, life is in extreme danger. As soon, however, as the ligature is untwisted and the passage through the pulmonary artery thus opened up, the arterial pressure-curve reascends (its pulsations succeeding each other at first slowly, but by degrees more rapidly) till it, as a rule, reaches, and for a short time maintains, a level higher even than the original, while at the same time the level of the soda-manometer falls almost to the zero point.

You see, the last part, the conclusion of this experiment, harmonizes perfectly with the pericardial one, while the first part presents a complete contrast. For, while in the pericardial experiment, the lowering of arterial and the elevation of venous pressure were from the commencement exactly proportional to the increase of tension in the sac, stenosis of the pulmonary artery has, for a long time, no influence whatever on the circulation through the systemic vessels. An examination of the intracardiac curve affords an explanation of this striking difference. The moment the pulmonary ligature is tightened even slightly, *you observe an immediate rise of intracardiac pressure on the right side;* and the more the stenosis is increased, the higher is the ascent of the pressure-curve of the right heart. This is expressed most elegantly by the curve obtained from the maximum manometer; every turn of the rod, even the gentlest, is here at once responded to by a step upward. The manometer of ordinary construction also represents this appearance quite clearly. Indeed, it reveals another interesting phenomenon not observable in the maximum curve, namely, an extension of the systolic excursions of the mercurial column, keeping pace with the gradually increasing constriction. True, in the case of the right heart this extension is not very striking; yet, where the narrowing was extreme, I have sometimes seen the distance between the systolic summit and the diastolic depression almost doubled. The rise of intracardiac mean pressure, if one may use the expression, or the maximum values attained by the single systoles, is still more considerable; in severe narrowing they very commonly exceed the original maximum by two or three times its value. The intracardiac pressure reaches its greatest elevation at the moment when the arterial curve rapidly falls. At this point the ventricle makes what may be described as a series of desperate efforts, marked by long excursions corresponding with the heart-beats, which are now slow and rapidly become irregular. This does not last long, it is true; for the intracardiac pressure falls after a very short time whether the ligature be relaxed or not. If an extreme degree of stenosis be maintained, the intervals between the heart-beats become longer and longer, and the curve acquires the closest resemblance to the last part of the curve of asphyxia. If, on the other hand, the passage through the pulmonary be freed, a fall of pressure in the right heart takes place *pari passu* with a reascent of the femoral pressure, whereby the systolic excursions continue large at first, but quickly regain their original size and frequency.

If, instead of the pulmonary artery, the aorta ascendens be ligatured, the course of the experiment is in all essential particulars the same. Here also, the arterial and venous pressures are wont to remain a very long time completely unchanged, despite the steadily increasing narrowing of the aortic lumen, till at last the sudden and steep descent of the arterial curve and rapid ascent of the venous pressure ensue. Henceforward the femoral curve proceeds in a straight line, uninterrupted by respiratory- or pulse-elevations, and steadily approaches the abscissa, while the level of the venous manometer rises slowly but continuously. But when the aortic ligature is relaxed, the femoral pressure instantly shoots up, almost always in the first instance above its original level, which it, however, resumes after the lapse of about five to ten seconds; while the venous pressure is restored in a very short time to normal. Nevertheless, as compared with stenosis of the pulmonary artery, there are some peculiarities in the details which are worthy of being recorded. In the first place, there may occasionally be seen, sometimes preceding, sometimes following, the abrupt fall, an equally abrupt ascent of the arterial curve, never lasting long, it is true, but very soon giving place to the final descent already described—without doubt the effect of acute anaemia of the brain, which produces, as you are aware, intense excitement of the vasomotor centre. Moreover, in the aorta the earliest beginning of the gradual

* Goltz and Gaule, 'Pflüg. Arch.,' xvii. p. 100.

stenosis does not manifest itself, as was the case in the pulmonary artery, by an increase of intracardiac pressure; the twist given to the ligature-rod must be somewhat more ample before the heart reacts to it—to be explained, I think, by the circumstance that a slight diminution of the lumen of the aorta is of no importance when compared with the sum of the resistances normally opposed to the emptying of the left ventricle. But when once the heart's action is affected, the increase in intracardiac pressure is much more considerable, not only absolutely but relatively, than on the right side; so that I have repeatedly observed an ascent of maximum pressure to four times the value of that obtaining with a free aortic channel. Of surpassing interest, however, is the influence of the stenosis of the aorta on the character of the individual cardiac contractions, and thereby on the arterial pulse. The narrower the aortic lumen and the higher the intracardiac pressure, *the more ample do the single contractions become,* and the greater, consequently, the distance between the systolic summit and the diastolic depression of each pulsation. At first no more time is consumed by these enlarged cardiac contractions than formerly; but when they exceed certain limits, they cannot possibly be carried out unless more time be expended on the single contractions; or, in other words, as soon as the stenosis has attained a certain pitch, the heart-beats become considerably more ample, but also *slower, less frequent*. A change of this kind must naturally have its effect on the arterial curve, and it may in fact be observed that, after a certain amount of twist has been given to the ligature, the systolic elevations of the femoral artery become fewer, and, to compensate for this, a good deal larger and less steep in their ascent; *there is an infrequent and sluggish, but mostly elevated pulse* . . .

But however remarkable this feature may be, for us the chief interest of experimental stenosis lies in the circumstance that it affords the key to the comprehension of cardiac pathology. For you will certainly have no hesitation in utilizing the experiences gained here, not merely in artificial insufficiency of the aorta, but also in the natural valvular and other lesions which impose an abnormal amount of work on the heart. If, in the previously normal aortic valves of individuals advanced in life, or in younger individuals, after an inflammatory process leading to adhesion of the valvular segments has run its course, a pure, uncomplicated aortic stenosis be developed as the result of a high degree of calcification of the segments, the condition produced is not to be distinguished in any essential particular from our artificial narrowing except by its much more gradual establishment, its chronic character; this, however, is a circumstance, which certainly cannot be anything but serviceable to the discharge of the work of the heart. Yet we are not left to infer from experimental evidence alone that the human heart reacts to the pathological valvular lesions simply by increasing the work done; we have, in addition, an infallible proof of this in *the increased bulk, the hypertrophy* of the heart, or of that portion of its musculature at least, on which the lesion in question throws a larger amount of work . . .

Comment on Cohnheim's Experiments

The foregoing excerpts are part of a treatise on pathology significantly titled *Lectures.* The arrangement of this work is of interest. Its first two major subdivisions are titled, respectively, "Circulation" and "Nutrition." Whereas "Circulation," as a modern reader might expect, discusses the heart, peripheral resistance, thrombosis, embolism, dropsy, and the like, "Nutrition" includes necrosis, atrophy, hypertrophy and tumors.

In his introductory chapter, not included in the present excerpts, Cohnhein says, "We speak of disease only when we have an *occurring,* a *progression,* a *process* in mind . . . This consideration, it is evident, leads us logically to define disease as a *deviation from the normal or healthy vital processes.*" The emphasis is clearly dynamic; hence, the importance of experiments on the living animal. From the large number of experiments Cohnheim performed I have selected a few examples dealing with the valves and chambers of the heart, since these lead directly to the work of MacCallum and others which will be considered later in the present series.

Cohnheim produced aortic insufficiency by lacerating the aortic valves with a metallic sound introduced by way of the carotid artery. The results were studied by auscultation and determinations of arterial pressure. Finding this blind procedure inadequately controllable, Cohnheim turned to operations on the pulmonary artery and aorta. In curarized dogs maintained under artificial respiration he placed ligatures loosely about both of these vessels while keeping manometric surveillance of arterial, venous and intracardiac pressures. Occlusion of the pulmonary artery had no effect on jugular or femoral pressures until stenosis had been carried beyond a certain degree. After this the level of arterial pressure fell steeply while venous pressure increased. These events contrasted sharply with what happened after aortic occlusion.

Apart from the obvious importance of Cohnheim's work—with which we must include that of his many pupils—Cohnheim has special importance for us as Americans, since he was a teacher of William Welch and was influential in Welch's appointment to the professorship at Johns Hopkins. Since Welch may be regarded as the father of experimental pathology in the United States, Cohnheim may be designated its grandfather.

Cohnheim's influence on American pathology did not end with Welch. His writings influenced MacCallum, in a manner that will be discussed later in the present series.

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Principles and Pitfalls in Establishing Normal Electrocardiographic Limits

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The three main prerequisites for determination of valid normal limits are adequate sample size, sample composition representative of the average healthy population, and adequate statistical evaluation. In a substantial number of publications, even recent publications, one or the other of these principles (and occasionally all three) have been disregarded. The most common error is inadequate sample size. The minimal sample size of a male adult population for determination of normal limits should exceed 500, and approach 1,000 for a mixed sample of men and women. Constitutional variables affecting the electrocardiogram (relative body weight, age, sex and race) must be considered. In view of the skewed distribution of most electrocardiographic items, 95 or 98 percentiles should be used for determination of valid normal limits. Use of standard deviations (usually ±2 SD) may result in erroneous limits. The extreme values of the distribution of a sample of healthy persons are not acceptable because they include values from a substantial number of abnormal persons, thus resulting in a large number of false normal diagnoses.

There are three prerequisites for determination of normal limits, (1) adequate sample size, (2) composition of the sample to be representative of average healthy population, and (3) adequate statistical evaluation.

Adequate Statistical Evaluation

Actual extreme values of a sample: The following statistical methods have been used for determination of normal electrocardiographic limits: (1) actual extreme values of a given sample (for instance, in the widely quoted limits of Sokolow and Friedlander[1]). This is the poorest method for the establishment of normal limits; the limits will expand with the size of the sample. In numerically adequate samples they are so wide that they include an appreciable number of patients with false normal diagnoses. On the other hand, extreme values in small samples may not include 95 percent of the normal population and thus may result in false diagnoses of abnormality. Extreme stray values in a large sample may well be due to unrecognized pathologic changes; these values should be excluded rather than included when normal limits are established. Therefore, the *total* normal distribution is not suitable. The limits should include the large majority of the normal healthy population, cutting off a small percentage of healthy people. Cutoff points of 2 or 2.5 percent at the low and high ends of the normal distribution, used in most investigations, include 95 or 96 percent of the normal population. Hence, a small percentage of healthy subjects (2 to 2.5 percent at each end) will fall, by definition, outside of the normal limits. If the distance from the 95 percent limits is still small, such subjects may be classified as "borderline," provided that only one item is concerned. If more than one item slightly exceeds the normal limits, the proba-

From Mount Sinai Hospital and the Laboratory of Physiological Hygiene, Minneapolis, Minn. This study was supported in part by Grant HL 11325 from the National Institutes of Health, Bethesda, Md. Manuscript accepted June 27, 1973.

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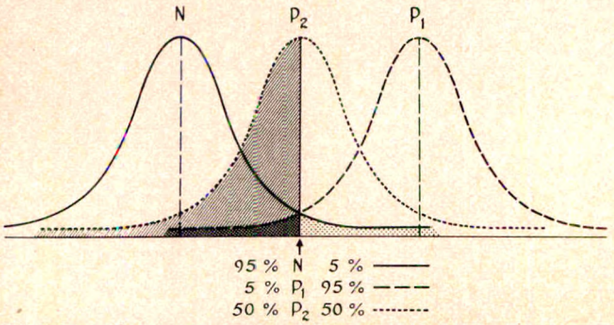

FIGURE 1. Frequency distribution of a hypothetical normal sample (N) and two samples of patients (P_1 and P_2) representing two different types of disease for a hypothetical electrocardiographic item. The dividing line for 5 percent at the upper end of the normal distribution coincides with that for 95 percent of the patients in group P_1 and for 50 percent (median) in group P_2. The areas of overlap are shaded. The diagnostic implications are discussed in the text. (Reprinted by permission from Simonson E: The normal variability of the electrocardiogram as a basis for differentiation between "normal" and "abnormal" in clinical electrocardiography. Am Heart J 55:80–103, 1958.)

bility of abnormality increases.[2] In general, the probability of abnormality increases with the distance of a subject from the mean or median of the distribution inside and, particularly outside, the 95 percentile limits. There is always some overlap in the distribution of diagnostic items in a normal population and in a population of patients limiting the diagnostic separation. The degree of overlap depends on the type of abnormal condition and its severity, and on the diagnostic item. As a rule, more patients will be within the normal 95 percent distribution range than the small number of 4 to 5 percent healthy subjects falling outside.

As an example, the overlap in the distribution of "normal" subjects and patients with left ventricular hypertrophy by QRS scalar or spatial voltage criteria has been a frustrating experience of many investigators.[3] McCaughan et al.,[4] recently investigated the rate of electrocardiographic and vectorcardiographic recognition of left ventricular hypertrophy in 939 patients with arterial hypertension subdivided into three groups progressing in severity of disease (group 1—394 patients; group 2—242 patients; group 3—303 patients). In their study, use of the voltage criterion 3.1 of the Minnesota code[5] for the conventional electrocardiogram provided a correct diagnosis in only 21 percent of cases in the first group, 34 percent of cases in the second group and 43 percent of cases in the third group, with a false positive rate of 6 percent. Conventional Frank lead criteria ($R_x - 1.9$ mv; $R_x + Sy - 2.1$ mv; $R_x + S_z - 3.1$ mv) were somewhat superior with a 24 percent rate of correct recognition of left ventricular hypertrophy in group 1, a 37 percent rate in group 2 and a 44 percent rate in group 3. False normal rates were 76, 63 and 56 percent, respectively, and the false positive rate was 5 percent for all three groups. The differentiation was still unsatisfactory but could be improved by multivariate analysis. The situation is schematically illustrated in Figure 1, which shows the frequency distribution of a hypothetical item in a hypothetical normal sample (N) and two samples of patients (P_1 and P_2) representing two different types of disease. For simplicity, a symmetrical Gaussian distribution has been assumed. The dividing line for 5 percent at the upper end of the normal distribution (marked with an arrow) coincides with that for the lower 5 percent of the patients in group P_1 and with 50 percent (median) in group P_2. The areas of overlap are shaded. The normal limits are the same for comparison of N with P_1 and P_2, but the diagnostic separation is very different: excellent for P_1 and poor for P_2. Unfortunately, the situation in group P_2 is more common, whereas that in group P_1 is quite exceptional, as Weisbart and Simonson[6] demonstrated for various electrocardiographic items in differentiating a normal population from a sample of patients with inferior myocardial infarction.

Figure 2 shows the distribution of the Q_3 interval in a normal sample and in a sample of patients with inferior wall infarction (old, subacute and acute). There is a wide overlap, corresponding approximately to that of groups N and P_2 in Figure 1. The overlap is even greater for Q_3 amplitude (Fig. 3). On the other hand, the separation in the distributions of T_2 (Fig. 4), particularly in subacute inferior infarction, is quite good, approximating the situation of N vs. P_1 in Figure 1. Unfortunately, this is exceptional; overlap as in the distribution of Q_3 is more common.

Standard deviation: Two methods have been used to determine the 95 percent normal limits: (1) more frequent, addition of ±2 standard deviations (S.D.) to the mean, and (2) less frequent, determination from the percentile distribution. Use of the standard deviation for determination of normal limits is convenient, but this method assumes a symmetrical Gaussian distribution. Unfortunately, nearly all single electrocardiographic items as well as ratios (such as Q/R ratios) have highly skewed distributions.[7]

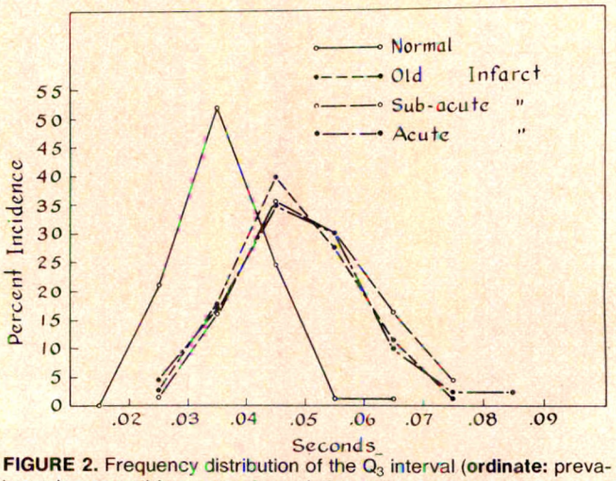

FIGURE 2. Frequency distribution of the Q_3 interval (**ordinate:** prevalence in percent) in a normal population and in patients with myocardial infarction of the posterior wall (acute, subacute and old). (Reprinted by permission from Weisbart and Simonson.[6])

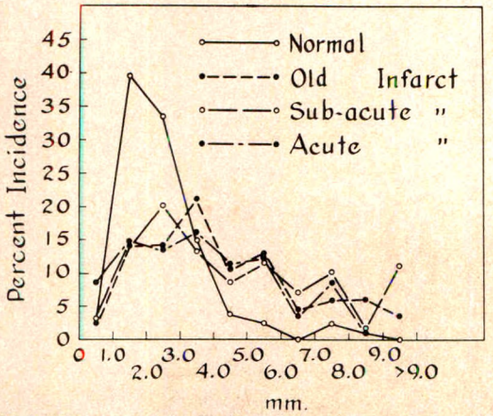

FIGURE 3. Frequency distribution of the Q_3 amplitude (**ordinate:** prevalence in percent) in a normal population and in patients with myocardial infarction of the posterior wall (acute, subacute and old). (Reprinted by permission from Weisbart and Simonson.[6])

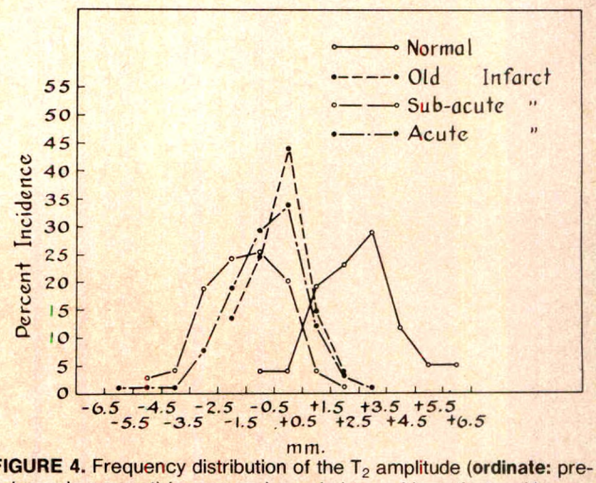

FIGURE 4. Frequency distribution of the T_2 amplitude (**ordinate:** prevalance in percent) in a normal population and in patients with myocardial infarction of the posterior wall (acute, subacute and old). (Reprinted by permission from Weisbart and Simonson.[6])

Therefore, normal limits determined with use of ±2 S.D. are too narrow at the long end of distribution and too wide at the short end, resulting in an appreciable number of false normal diagnoses at the short end and false abnormal diagnoses at the long end of distribution.

Percentile distribution: Determination of normal limits from the percentile distribution is the only reliable method for establishing normal limits. This procedure is facilitated by utilizing electronic computer analysis from punch cards. However, a simple method without aid of computers has been described by Barden (Appendix 1, p 285, in Simonson[7]). I will discuss some more sophisticated aspects of statistical analysis later.

Sample Size

Of the pitfalls in determination of normal limits, inadequate sample size is probably the most frequent.[7] Even in a relatively homogenous sample, such as a sample of young men aged 20 to 30 years with normal body weight, that is, between 95 and 105 percent of predicted body weight (normal = 100), at least 100 subjects are needed for recognition of the percentile distribution, and the normal limits derived would be applicable only to a similar homogenous sample in regard to age, body weight and sex. All constitutional variables—age, body weight, sex, race and, to a lesser degree, chest configuration—are determinants for the normal electrocardiogram.[7–9] Whereas the individual electrocardiograms of older and younger, underweight and overweight, male and female subjects may fall well into generally accepted normal limits, the distribution of the various items and, consequently, the normal limits will be different in samples with different proportions of these constitutional variables. Therefore the sample must be large enough to cancel out or, preferably, permit separate analysis of the effect of the various constitutional variables on the distribution of electrocardiographic or other items in the subgroups thus defined. The purpose of the subdivision into categories of age, relative body weight, sex and race is to provide the normal limits for these subgroups, which are considerably narrower than the limits for the whole population sample and provide a more accurate separation between "normal" and "abnormal." Thus, each individual patient should be evaluated with use of the normal limits for his constitutional category.

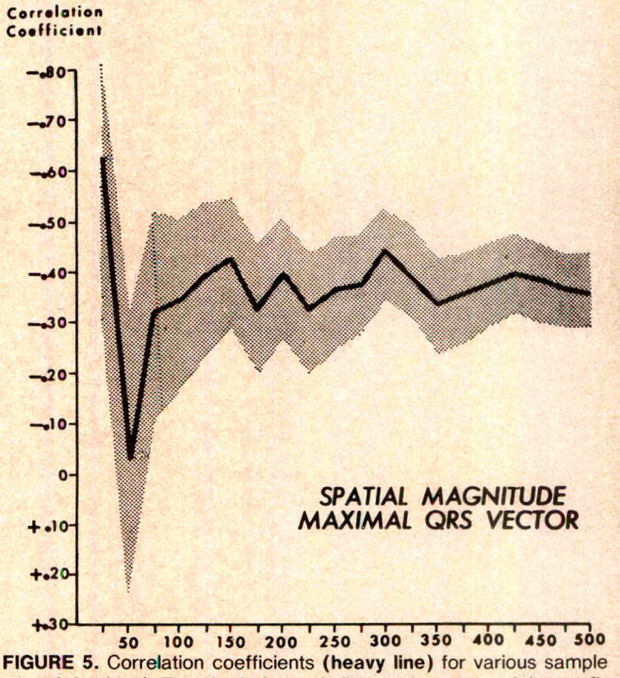

FIGURE 5. Correlation coefficients **(heavy line)** for various sample sizes **(abscissa).** The **shaded area** indicates the extent of the confidence limits. (Reprinted by permission of the American Heart Association, Inc. from Pipberger et al.[10])

The need for a large sample size has been demonstrated by Pipberger et al.[10] Figure 5 shows the variation of the correlation coefficient *(r)* between age and the spatial maximal QRS vector. Small sample sizes, that is, up to 200, show huge variations, and the cor-

relation coefficient stabilized only with sample sizes over 500. It is not surprising that with groups of less than 200, as were frequently used in studies of the effect of age on the electrocardiogram or vectorcardiogram, conflicting results have been obtained.[11] Thus, the minimal sample size for determination of normal limits of the male adult population should exceed 500 and should be closer to 1,000 if the sample includes men and women. Assuming three age and three weight groups of an adult male and female population with 100 in each subgroup, we arrive at a desirable sample size of 1,800. Our sample of 950 adult men and women[7] did not permit subdivision of the female sample and the young male sample into weight groups. Such subdivision is desirable, if not essential, since the effect of age is different in men and women and the effect of relative body weight is greater in older than in younger people. Because of the skewness of distribution, constitutional variables may affect upper and normal limits differently. For example, the left QRS axis shift with age affects much more the lower (2.5 percentile) than the upper normal limits (97.5 percentile). In men, the upper normal limit for ages 20 to 29 years is 95.9° and at ages 40 to 59 it is 87.9°, a difference of 8°. The low normal limits change from 2.9° to −28.4°, respectively, a difference of 30.9°.[7]

The largest sample (6,014 healthy men) with measurement of electrocardiographic items has been collected by Hiss et al.[12] However, clinical application of their data is limited because many of the measurements are unconventional and some items used in clinical routine are not included. Several attempts have been made to arrive at a large sample size by pooling samples.[13–16] This is not a sound procedure. Limits from pooled samples are likely to be determined largely by samples that are least representative of the healthy average population. The most recent example of inadequate sample size is found in the study by Copeland et al.[17] Normal 95 percent limits were calculated for the McFee-Parungao vectorcardiogram from a sample of 120 normal subjects (61 men, 59 women) with an age range of 15 to 64 years. The age distribution was highly skewed and no information about weight and race distribution was given. It is unlikely that the values can be reproduced in another normal sample with a different distribution of age, sex, weight and race.

Sample Composition

The sample shold be representative of the healthy, average American population. Obviously, even a large sample, such as that collected by Hiss et al.,[12] is a very small portion of the total population. Several precautions are needed to assure reasonably adequate sample composition. For male populations aged 20 to 60 years, the sample should be drawn from a working population since this is the large majority and its use facilitates collection. The civilian female labor force in the United States is about 50 percent of the adult female population and therefore should be fairly representative.

Electrocardiographic screening process: To obtain a sample representative of the average *healthy* population, the sample must be screened for elimination of all subjects with chronic diseases that could even remotely affect the electrocardiogram; fourteen such conditions have been listed.[7] The screening should be done independently; that is, it should not involve the electrocardiogram. This leads to a dilemma, because the electrocardiogram is a more sensitive method for detecting myocardial disease than most other routine methods. According to the Framingham study, about 30 percent of myocardial infarctions are silent. Bundle branch block, particularly right bundle branch block, may be clinically asymptomatic. For detection of arrhythmias the electrocardiogram is the only available objective method. Coronary arteriography is obviously not suitable for collection of a large normal sample. Therefore, it has been an accepted and justifiable procedure to exclude from normal samples all subjects with gross electrocardiographic abnormalities. The Minnesota code,[5] which is being widely used on an international scale, is a useful tool for this purpose. For data on prevalence of electrocardiographic abnormalities in a large asymptomatic population we refer to Averill and Lamb's study[18] on 63,375 Air Force personnel, and to the large epidemiologic series of Keys.[19]

Clinical screening process: The definition of health is a difficult problem because it is based on a negative criterion: the absence of recognizable disease. A person should be considered healthy when results of all clinical tests that may reveal disorders potentially affecting the electrocardiogram are negative. The distribution of the various items in a group thus selected could then be taken as representative for a healthy population. Unfortunately, the clinical screening procedure has not been standardized; its reliability depends on the methods used, as well as on the thoroughness and experience of the clinical investigator. The examination should include a thorough history, which may be facilitated by questionnaires such as those prepared by members of the Laboratory of Physiological Hygiene. The individual electrocardiogram in many pulmonary, hormonal, infectious, central nervous system and even cardiac diseases may be within the normal range of limits, but in all these conditions electrocardiographic abnormalities have been reported. Therefore, inclusion of such patients will invalidate the "normal" limits.

Pitfalls in sample selection: A common pitfall is the use of "cardiovascular normal" hospitalized patients. Hospitalized patients, whatever the reasons for hospitalization, are not representative of the healthy average population. Bed rest alone produces a deterioration of cardiovascular regulations in young, healthy men.[20,21]

Similarly, electrocardiograms obtained before death from hospital patients with a normal heart at

autopsy are not a suitable source for a normal sample, unless obtained from accident victims. Absence of detectable cardiac disease does not rule out functional ST–T segment changes or arrhythmias. The sample of Myers et al.,[22] used for normal electrocardiographic standards, consisted of moribund patients with a normal heart at autopsy. It is hard to conceive of a sample more remote from the healthy average population.

We found significant differences between the means of various electrocardiographic items in Vaquero's sample[23] and our sample of 950 adults in the United States. Therefore, the normal limits from the Mexican sample are not applicable to the American white adult population, but were utilized in the pooled samples.[13–15] We also found significant differences between various electrocardiographic items in American and Italian populations[24] and Japanese population.[2] Therefore, standards obtained in one country may not be applicable for populations of other countries. For large countries such as the United States, wide geographical distribution of the sample is desirable. This was achieved in our sample.[7] Reservations must also be made about samples obtained from a population preselected for physical fitness, such as athletes and (to a lesser degree) military personnel.

Nearly every conceivable pitfall can be found in the sample of Sokolow and Friedlander.[1] In view of the extreme heterogeneity of the sample (including psychiatric patients, aviation personnel and even some infants), its size (150) is much too small. The use of actual extreme values for the normal limits is not acceptable, as discussed earlier. The limits are most likely determined by extremes in the sample.

Even a large sample collected with an attempt to avoid all pitfalls may not be truly representative of a general healthy population because it is rarely possible to obtain a truly random sample of the total population. Comparison with other samples of healthy persons collected independently by other investigators in different regions would be important for generalization. There is excellent agreement between the limits in our sample of young men and those in the original sample of 1,000 young men of Graybiel et al.,[25] and between the longitudinal electrocardiographic age trends of the 17 year follow-up study[26] of their original sample and the cross-sectional age differences in our male sample of 649 men. This agreement gives assurance that both samples are fairly representative of the healthy, male adult American population.

Separation of "normal" and "abnormal": In view of the overlap in the distribution of single electrocardiographic items in healthy populations and various populations of patients, the relation between two or more electrocardiographic items has been used to improve the separation between "normal" and "abnormal." The simplest relations are ratios such as R/S, Q/R, R/T and P/R ratios. Frontal plane QRS, T and P axes also reflect the relation between two variables. Utilization of these ratios for normal limits has considerably improved the correct recognition of various abnormalities. The percentage in patients of Q/R ratios exceeding 95 percent of normal limits exceeded that of Q wave amplitudes or duration in Frank leads Y and Z.[27] With use of a more sophisticated statistical method, sets of Q/R ratio limits were prepared for three Frank leads on the basis of the respective probability density function for a population of healthy men and 114 patients with myocardial infarction. The combined use of normal limits for a Q/R ratio of 0 to 0.19 mv in lead X, 0 to 0.24 mv in lead Y and 0.1 to 1.64 mv in lead Z resulted in correct recognition of 77.2 percent of patients with infarction, independent of site of the infarct and with a false abnormal rate of only 0.2 percent. Q wave amplitude contributed practically nothing to the separation obtained by means of Q/R ratios.

Normal 95 percent limits determined by bivariate analysis, utilizing the initial frontal plane 20 msec QRS and maximal QRS vectors, increased the recognition of myocardial infarction from insignificant (17.5 percent) for the single vectors to clinically useful (71.1 percent).[28]

Multivariate analyses: One of the first attempts to use multivariate analysis was undertaken by Shapiro et al.[29] In 649 healthy men and 516 asymptomatic men with hypertension and a normal electrocardiogram, the Hotteling T^2 test was used to provide more sophisticated definition of normal limits and improved separation of these two groups. With a matrix of only five electrocardiographic items, 13 percent of the hypertensive group were outside the 95 percent limits for normal. With 20 electrocardiographic items as a matrix, 40 percent of the hypertensive patients were outside these limits. The results were encouraging for systematic use of internal consistency among various electrocardiographic items to gain a more precise definition of normality. Recently, Pipberger and co-workers[4,30,31] did pioneering work in using multivariate analysis with the aid of electronic computers. The improved definition of normality greatly reduced the overlap in various abnormal conditions. We also have been working in this direction, and recently provided[32] a demonstration of the diagnostic power of this approach in the differentiation between anterior myocardial infarction and cor pulmonale. It is well known that the electrocardiogram in patients with cor pulmonale may simulate that of patients with myocardial infarction. Separation of these groups is far more difficult than separation of either group from normal subjects. By means of multivariate analysis the combination of five manually measured items—sum of R waves in leads X and Z, QRS interval, Z component of the 25 msec QRS vector, and the ratio $S_x/R_x + S_x$—resulted in correct identification of 89 percent of patients with cor pulmonale and 91 percent of patients with myocardial infarction. This recognition rate was far superior to that of single conventional or Frank electrocardiographic items. Kerr et al.[33] obtained similar results.

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Echocardiographic Manifestations of Discrete Subaortic Stenosis

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The echocardiographic manifestations of discrete membranous subaortic stenosis are described in three cases. The diagnosis was confirmed by cardiac catheterization in all and at operation in two. The characteristic finding in these patients was abnormal movement of the aortic valve leaflets. The leaflets opened rapidly with the onset of systole, then exhibited abrupt premature closure shortly after ventricular ejection. The valve remained partially closed throughout the remainder of systole. This premature leaflet closure is believed to be caused by obstruction to aortic valve flow produced by the band-like fibrous subaortic tissue. The valve leaflets also exhibited a gross fluttering motion possibly caused by a jet stream effect of the turbulent blood hitting the leaflets. In the two patients treated surgically, postoperative echograms continued to show premature leaflet closure but the degree of closure was decreased. The echocardiogram of one patient had the characteristic systolic anterior bulge of the mitral valve observed in muscular subaortic stenosis or idiopathic hypertrophic subaortic stenosis. Our data suggest that the following echocardiographic findings are suggestive if not specific for discrete subaortic stenosis: aortic valve closure early in systole, persistent valve closure throughout the remainder of systole, coarse fluttering of the leaflets, and absence of asymmetric septal hypertrophy.

Subaortic obstruction to left ventricular outflow has been generally classified in two categories: discrete membranous subaortic stenosis and idiopathic hypertrophic subaortic stenosis. Several echocardiographic features of idiopathic hypertrophic subaortic stenosis, sometimes called hypertrophic obstructive cardiomyopathy, have been described.[1–5] These features consist of systolic bulging of the anterior leaflet of the mitral valve and asymmetric hypertrophy of the septum. A few investigators[6] have noted systolic closure of the aortic valve. Discrete membranous subaortic stenosis is typically characterized by a ring-like fibrous band usually located immediately below the aortic valve. This paper describes the echocardiographic findings in a series of three patients with the diagnosis of discrete subaortic stenosis.

Material and Methods

The diagnosis of discrete subaortic stenosis was made in all three patients on the basis of typical findings at cardiac catheterization and cineangiography; in two patients operation confirmed the lesion. The three patients were aged 8, 18 and 18 years, respectively; two were male and one was female. The resting subaortic gradient was 90 and 100 mm Hg, respectively, in the two patients who underwent operation. The third patient had a gradient of 46 mm Hg and was not operated upon. Two patients had associated mild aortic insufficiency.

The echocardiographic examination was performed with an Ekoline 20 echograph combined with an Electronics for Medicine strip chart recorder. A

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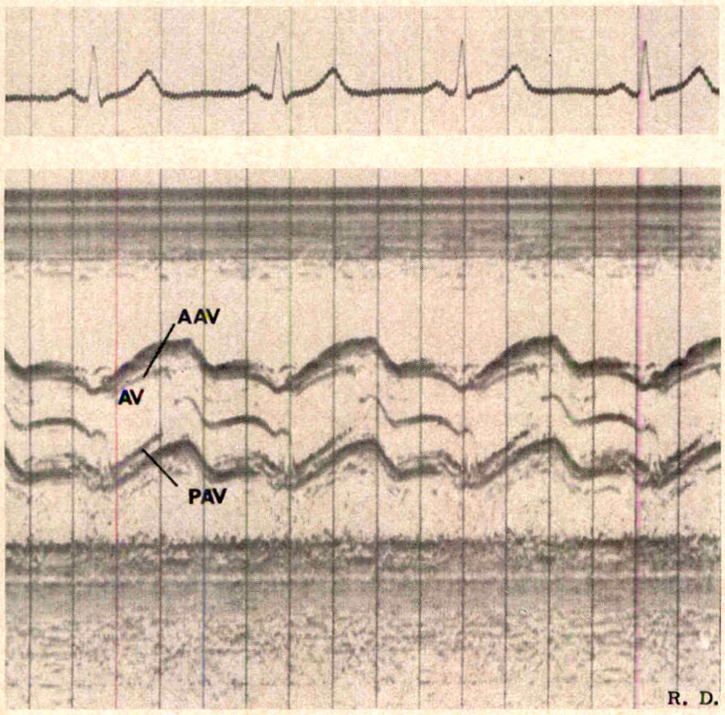

FIGURE 1. Normal aortic valve (AV) echogram showing opening of the valve leaflets with parallel separation throughout systole forming a box-like configuration. AAV = anterior aortic valve leaflet; PAV = posterior aortic valve leaflet.

2.25 megaHertz transducer with an outer diameter of 0.5 inch focused at 7 cm was used. All patients were examined in the recumbent position with the transducer placed in the third or fourth intercostal space along the left sternal border. With the transducer in this location the ultrasonic beam was directed so as to record a complete study of the mitral valve, left ventricle, aortic valve and the outflow tract including the aortic leaflets.

Results

All three patients had a striking abnormality of the aortic valve leaflets. In all, an initial rapid opening was followed by an abrupt closure of at least one leaflet shortly after the onset of ventricular ejection with continued partial closure or limited opening of the valves throughout the remainder of systole. There

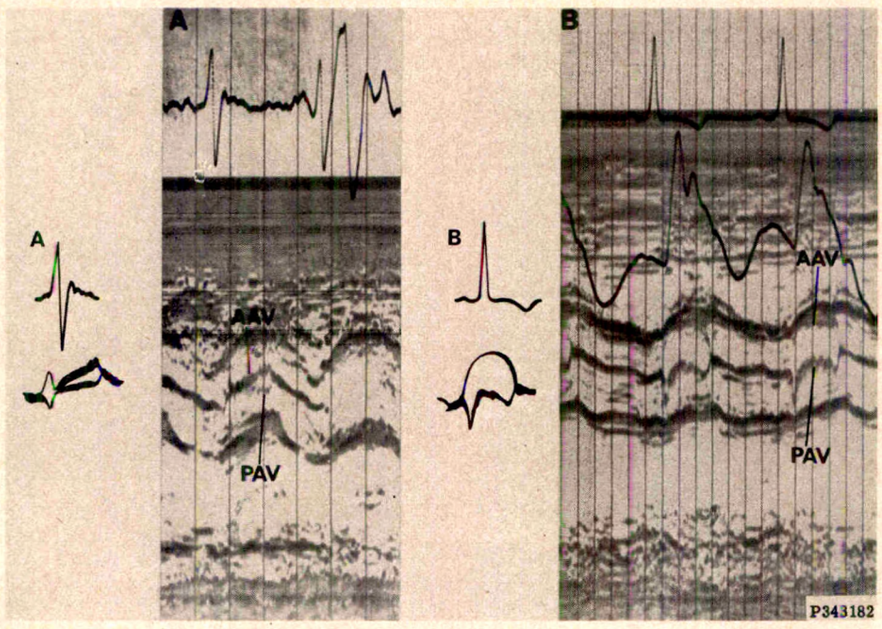

FIGURE 2. Case 1. **A,** preoperative echogram and accompanying diagram of the aortic valve echogram showing closure of the aortic leaflets in systole. **B,** postoperative echogram showing abnormal early closing but greater leaflet separation during systole. A carotid pulse tracing is superimposed on the echocardiogram.

was also a distinct fluttering of the aortic leaflets. Figure 1 demonstrates an echogram from a normal aortic valve. Shortly after the electrocardiographic QRS complex, the aortic leaflets open and form a box-like configuration throughout systole. These echoes originate from two of the three leaflets of the aortic valve. During systole they are parallel and then close after the end of ventricular ejection. Upon close inspection one may note a very fine fluttering of the leaflets. Figure 2 demonstrates aortic valve echograms obtained before and after operation in a patient (Case 1) with discrete subaortic stenosis. To the left of the echograms are diagrams indicating the motion of the aortic leaflets. In the preoperative illustration (Fig. 2A) the aortic leaflets open with the onset of systole and then close almost immediately and are in a relatively closed position throughout systole. After surgical relief of the subvalvular obstruction (Fig. 2B), there is marked improvement in the valve motion. The posterior aortic leaflet retains its abnormal motion with mid-systolic closure; however, the anterior leaflet has a more normal appearance so that the distance between these two leaflets is considerably greater in the postoperative record.

Figure 3 presents aortic valve echograms obtained before and after operation in Case 2. Again in the preoperative record (Fig. 3A), the valve closes abruptly after the onset of ventricular ejection and is in a relatively closed position throughout systole. Upon close inspection one can appreciate gross fluttering of the aortic valve during systole. This fluttering is more obvious than that seen in a normal aortic valve. After operation (Fig. 3B), the leaflets again move more normally. Although there is still a small degree of mid-systolic closure, the leaflets are widely separated almost throughout systole. Figure 4 is an

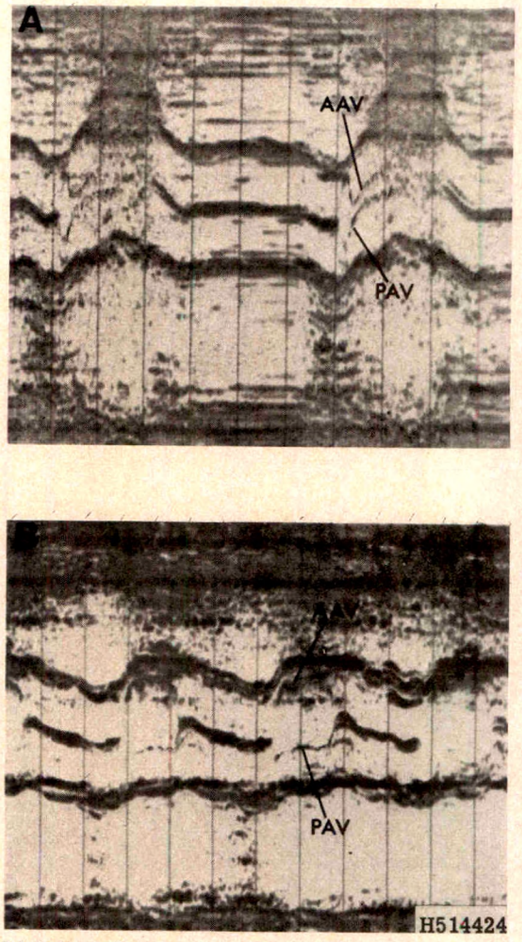

FIGURE 3. Case 2. **A,** preoperative aortic valve echogram showing early systolic closure of the valve leaflets. **B,** postoperative echogram with improved leaflet separation.

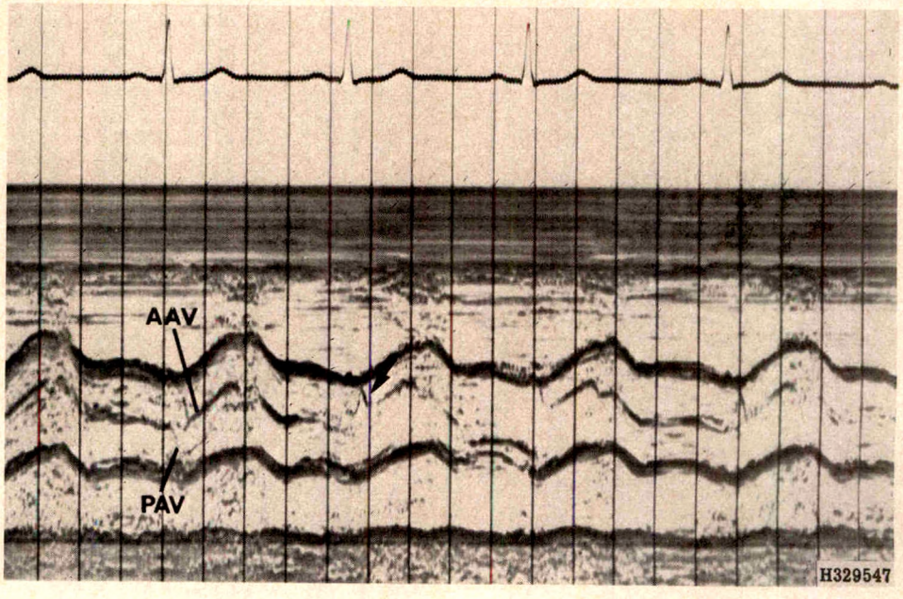

FIGURE 4. Case 3. Aortic valve echogram of the patient not operated upon. The **arrow** points to the distinctive early systolic closure.

aortic valve echogram taken from Patient 3, who had a gradient of only 46 mm Hg across the subaortic stenosis and was not treated surgically. Again only the anterior aortic valve leaflet is well seen, and one can detect the early systolic closure of the valve (arrow).

Discussion

As mentioned, mid-systolic closure of the aortic valve has been reported in patients with hypertrophic subaortic stenosis.[1–3] In our experience, this finding has occurred in patients with severe obstruction usually characterized by marked anterior bulging of the mitral leaflet to the point of virtually obliterating the outflow tract. Two of our three patients showed no evidence of systolic bulging of the anterior leaflet. We believe that close inspection of the echoes discloses some systolic bulging of the anterior mitral leaflet in one of the surgically treated patients. This bulging was not marked, did not obliterate the outflow tract and was not of the type usually associated with severe obstruction due to muscular hypertrophic subaortic stenosis. However, we cannot exclude the possibility that this patient had combined features of both discrete and muscular subaortic stenosis. After operation, the patient continued to have evidence of systolic bulging of the mitral valve despite a marked change in the aortic valve echogram. None of our patients had the asymmetric hypertrophy of the septum typical of hypertrophic subaortic stenosis.[5] All three patients had some degree of symmetrical hypertrophy of the left ventricle involving both the septum and the posterior left ventricular wall.

Some investigators[7] have mentioned that in this lesion it may be possible to visualize an abnormal echo in the vicinity of the outflow tract presumably originating from the site of obstruction. Although we observed some peculiar echoes in the outflow tract that may have originated from the obstructing lesion, we were not convinced that this was a reproducible finding in all three cases. This subject needs further investigation, and it is possible that we may be able to record the actual obstruction.

The abnormal aortic valve motion with discrete subaortic stenosis can probably be explained by alterations in aortic valve flow. The premature closure may be caused by the physical obstruction to aortic valve flow produced by the band-like fibrous subaortic tissue. Initially there appears to be rapid flow that produces some opening of the passive aortic leaflets. Possibly, as the left ventricle ejects its blood and the cavity decreases in size, the actual amount of obstruction increases and produces further diminution of aortic valve flow during much of systole. This degree of closure of the aortic valve during systole is rarely seen in patients with hypertrophic subaortic stenosis, who usually have only a brief period of closure during mid-systole. The fluttering of the leaflet seen in our patients is probably due to the jet of blood striking the leaflets. Although the normal aortic valve leaflets flutter slightly, the fluttering was far more pronounced in our patients.

Although our series of patients is small, we believe that the findings involving the aortic valve in patients with discrete subaortic stenosis are consistent. Since the abnormality seemed to be partially relieved after operative correction, it must be related to the subaortic obstruction.

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Echocardiographic Diagnosis of Left Atrial Myxoma

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The presence of a left atrial myxoma in a young woman who presented with mitral valve obstruction was established by echocardiography before surgery. A systematic echocardiographic approach to such a patient is described, by which other diagnostic possibilities, including artifacts, may be eliminated. It is indicated that echocardiography should be performed in patients with suspected obstructive lesions at the mitral valve, unexplained syncope or suspected bacterial endocarditis, as well as in patients who have had atrial myxomas removed since these tumors occasionally recur.

Echocardiography is rapidly becoming established as a reliable and safe technique for the diagnosis of atrial tumors.[1-6] Artifacts, atrial thrombi and mitral valve disease can cause difficulty in diagnosis. Nevertheless, if clinical evidence of mitral valve obstruction exists, a correct diagnosis of left atrial myxoma is possible from ultrasound tracings alone, provided a systematic approach to diagnosis is used. Such an approach is illustrated with echocardiographic recordings from a young woman with a left atrial myxoma.

Case Report

A 30 year old woman was referred to the Tulane Cardiology Service at Charity Hospital of Louisiana at New Orleans for mitral commissurotomy. Dyspnea on exertion, orthopnea and occasional dizziness had begun insidiously 8 years before admission, during the last trimester of her third pregnancy. Steady worsening of her symptoms began approximately 4 months before admission. There was a questionable history of low-grade fever, but there was no history of rheumatic fever. During March 1972, the patient underwent cardiac catheterization at another hospital. The data were considered to show mitral stenosis and pulmonary hypertension, and mitral commissurotomy was recommended.

Physical examination on admission to Charity Hospital showed a blood pressure of 110/70 mm Hg, pulse rate of 68 beats/min and temperature of 98.4° F, orally. Regular sinus rhythm was present, and the apex beat of the heart was located in the fifth intercostal space in the midclavicular line. The first heart sound could be palpated at the apex, and a left parasternal impulse was present. On auscultation, the first heart sound was loud at the apex. The second heart sound at the base was narrowly split and had an accentuated pulmonic component. A low-pitched, early diastolic sound, best heard at the apex, was well separated from the second heart sound and did not have the quality of an opening snap. A grade 2/6 high-pitched systolic murmur that radiated to the axilla and a diastolic rumble with presystolic accentuation were heard at the apex. The diastolic rumble closely followed the early diastolic sound. A firm and nontender splenic tip was palpated.

Upon admission, the hematocrit was 35 percent and the hemoglobin 12.4 g/100 ml of blood. The erythrocyte sedimentation rate was 36 mm in 1 hour. Results of other laboratory examinations were within normal limits.

Teleoroentgenograms of the chest (Fig. 1) showed a heart with a "mitral" configuration. The pulmonary artery, left atrium and right ventricle were enlarged. The electrocardiogram (Fig. 1) was compatible with mild right ventricular hypertrophy and left atrial enlargement. An apex cardiogram

From the Department of Medicine of the Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans. This study was supported by Grant HL-06769 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md., the Rudolph Matas Memorial Fund for the Kate Prewitt Hess Laboratory, the Rowell A. Billups Fund for Research in Heart Disease and the Feazel Laboratory. Manuscript accepted June 11, 1973.

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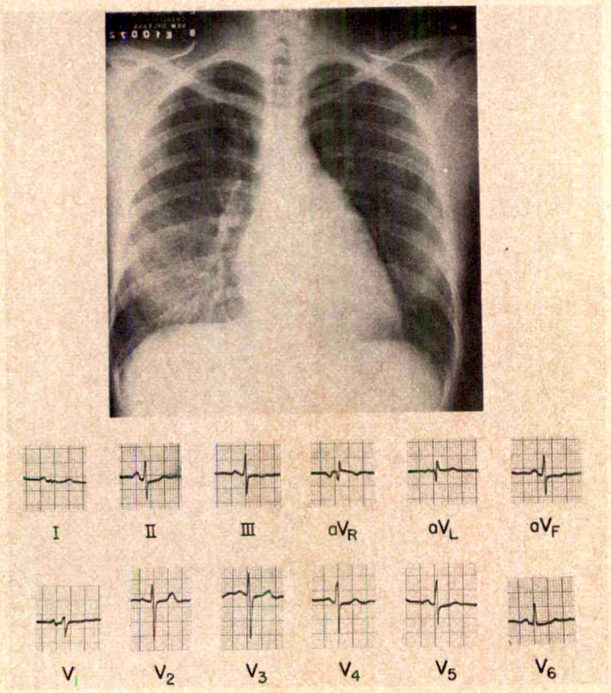

FIGURE 1. Teleoroentgenogram of the chest and electrocardiogram. The teleoroentgenogram shows "mitralization" of the heart. The left heart border is straight, the primary pulmonary arterial segment is enlarged and the vascular pattern is increased in upper lung zones. The electrocardiogram is compatible with left atrial and mild right ventricular hypertrophy.

showed a deep notch in the systolic portion of the tracing, which coincided with the first heart sound.

Echocardiography: On the day after admission to the hospital the patient was examined with a Smith-Kline ultrasonoscope (Ekoline-20A). This instrument has a transducer 1.6 mm in diameter, a frequency of 2.2 megaHz and a repetition rate of 1,000 pulses/sec. A permanent record was obtained using a Honeywell Visicorder. The patient was examined in bed with her head elevated 30°. With the transducer placed over the fifth intercostal space at the left sternal border, and the beam of ultrasound directed posteriorly and slightly inferolaterally, echoes were recorded from both mitral valve leaflets and the posterior wall of the left ventricle (Fig. 2B). Clouds of wavy-lined echoes were recorded posterior to the anterior leaflet of the mitral valve only during ventricular diastole (Fig. 2B). The portion of diastole during which these tumor echoes were recorded varied greatly with both direction of the ultrasound beam and patient position. Echoes from the posterior leaflet of the mitral valve could be recorded only after careful exploratory scanning. Once these echoes were identified, a record could be obtained that showed echoes from both leaflets as well as abnormal tumor echoes (Fig. 2B).

With the transducer placed over the fourth intercostal space and the ultrasound beam directed posteriorly, echoes from the anterior leaflet of the mitral valve and from the posterior wall of the left atrium were recorded. In this position, clouds of wavy-lined echoes could be seen posterior to the anterior leaflet of the mitral valve in the left ventricle during diastole and in the left atrium during ventricular systole (Fig. 2C).

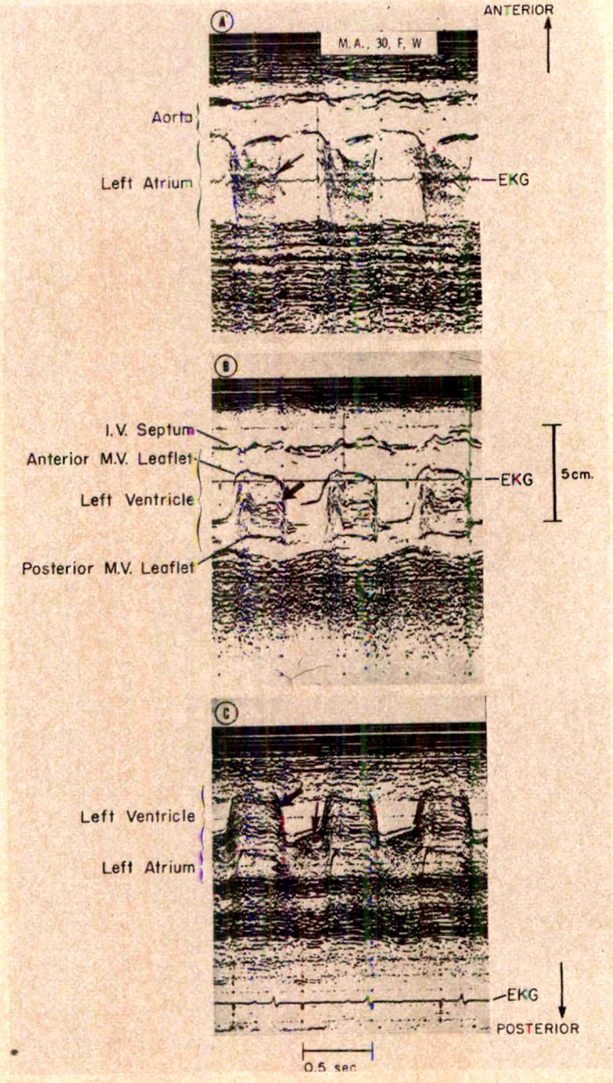

FIGURE 2. Echocardiograms recorded with the ultrasound beam directed **(A)** through the aorta and left atrium, **(B)** through the left ventricle and **(C)** through the left ventricle and left atrium. I.V. = interventricular; M.V. = mitral valve.

Finally, with the transducer still placed over the fourth intercostal space, but with the ultrasound beam directed toward the right shoulder, echoes were obtained from the aorta and left atrium (Fig. 2A). Clouds of abnormal echoes appeared in the left atrium only during ventricular systole. No echocardiographic abnormalities of the interventricular septum or left ventricle were recorded.

Recatheterization and surgery: The patient subsequently underwent a second right heart catheterization, and cineangiocardiograms of the left heart chambers were obtained by injection of contrast material into the pulmonary artery. A large filling defect detected in the left atrium was found to prolapse through the mitral valve orifice into the left ventricle during ventricular diastole (Fig. 3) and return into the left atrium during ventricular systole.

Finally, the patient had a typical myxoma excised from the left atrium (Fig. 4). Since recovery from operation, the patient has been asymptomatic. An echocardiogram recorded postoperatively showed normal findings (Fig. 5).

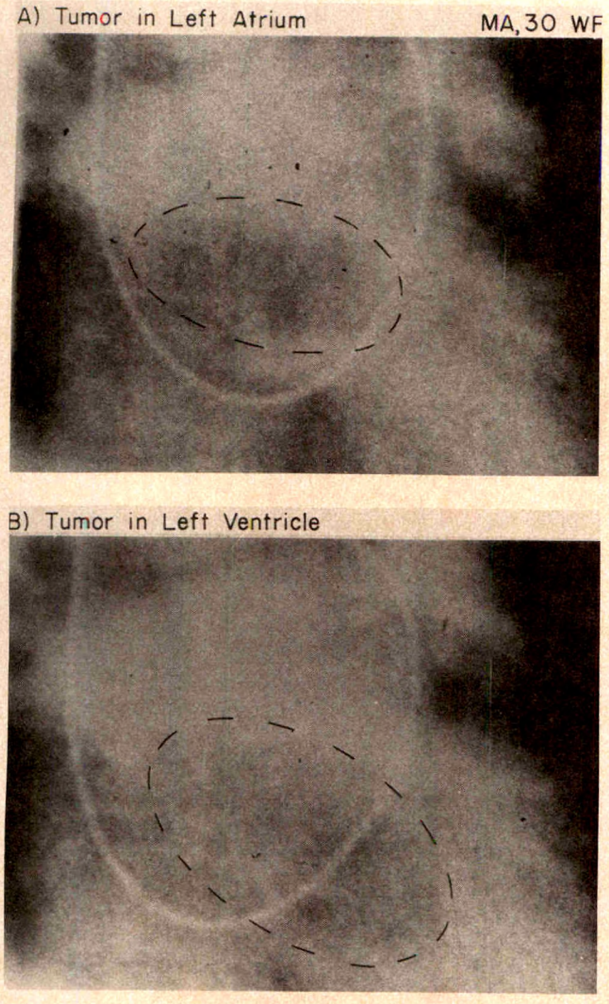

FIGURE 3: Cineangiograms recorded with the patient in the anteroposterior position during ventricular systole **(A)** and diastole **(B).** The "negative filling defect" representing the tumor is outlined.

Discussion

The clinical findings in this patient are familiar. Physical examination revealed ample evidence of pulmonary hypertension and a normal left ventricle. Together with electrocardiographic and roentgenologic evidence of left atrial enlargement, these findings were diagnostic of an obstructing lesion of the mitral valve orifice. The peculiar early diastolic sound and notching of the systolic portion of the apex cardiogram strongly suggested a left atrial myxoma.[5] The echocardiogram established the diagnosis.

Differentiation of left atrial myxoma and mitral stenosis: The echocardiographic examination of such a patient should be systematic. First, the presence or absence of mitral valve stenosis should be determined. The echocardiographic findings establishing the diagnosis of mitral stenosis are diminished C–E amplitude, decreased diastolic slope (E to F) and, in patients with regular sinus rhythm, absence of an *a* wave of the anterior leaflet of the mitral valve, as well as an inability to record echoes from the posterior leaflet of the mitral valve. The posterior leaflet moves concordantly with the anterior leaflet when mitral stenosis is present.[7,8]

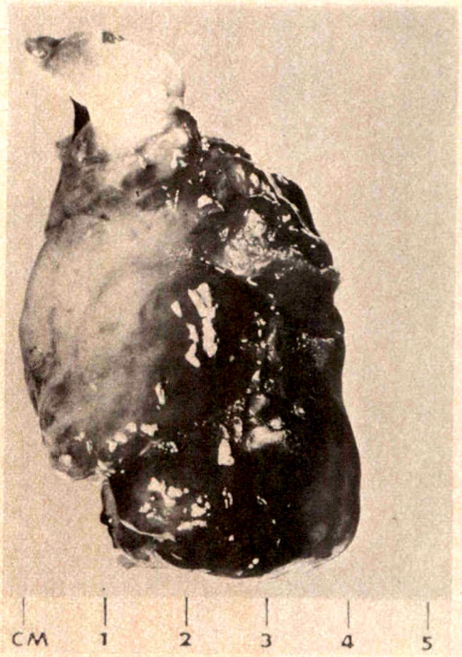

FIGURE 4. Photograph of myxoma removed surgically from the left atrium.

Thus, several features of the echocardiographic tracings obtained from patients with left atrial myxoma are useful in excluding the diagnosis of significant mitral stenosis, as illustrated by the tracings recorded from our patient. The most important echoes in excluding the diagnosis of mitral stenosis are those obtained from the posterior leaflet of the mitral valve.[8] Various planes may have to be explored to obtain clear echoes from the posterior leaflets, a procedure that often taxes the patience of both examiner and patient. However, the diagnosis of significant mitral valve stenosis may be excluded if the mitral valve leaflets can be demonstrated to move far apart during diastole. Additional evidence against the presence of mitral valve stenosis is a normal or greater than normal C–E amplitude. Although an *a* wave was present in the echocardiograms recorded from our patient, this finding does not exclude mitral valve stenosis.

A decreased E to F slope of the anterior leaflet of the mitral valve, as was occasionally recorded in this patient (Fig. 2B), should not by itself influence the examiner to make the diagnosis of mitral stenosis.[8] The flow of blood around the tumor mass and the absence of rapid pressure changes between the left atrium and left ventricle are probably responsible for the finding of a decreased E to F slope in patients with left atrial myxoma.

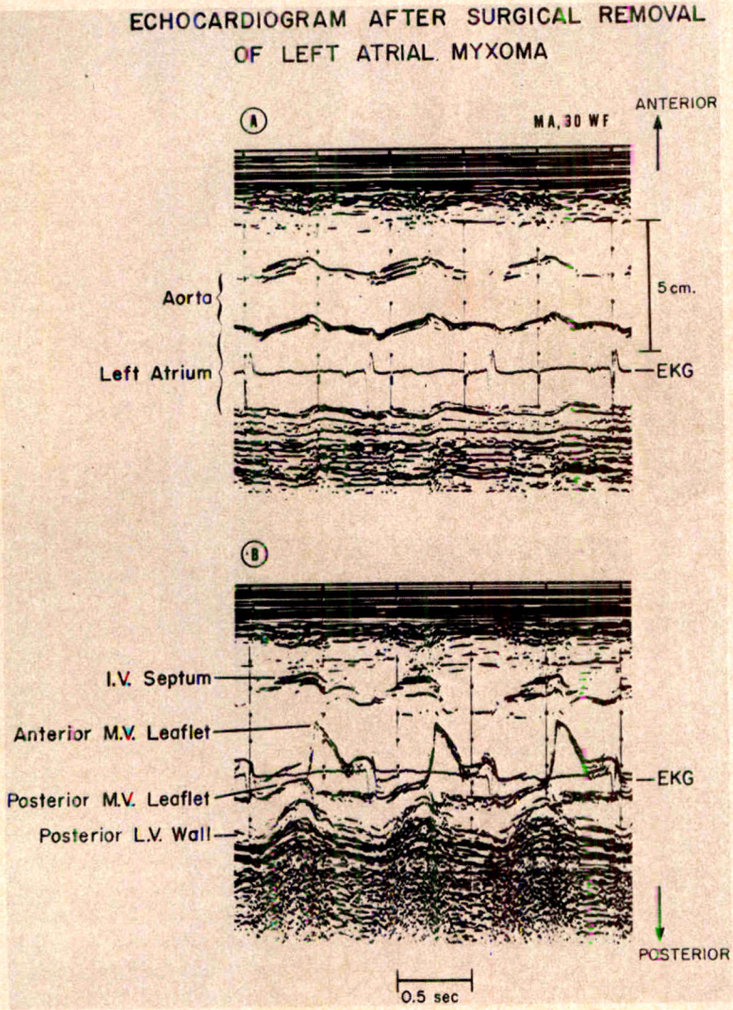

FIGURE 5. Echocardiograms recorded after surgical removal of the left atrial myxoma, with the ultrasound beam directed **(A)** through the aorta and left atrium, and **(B)** through the left ventricle. Compare these recordings with those shown in Figure 2. I.V. = interventricular; L.V. = left ventricular; M.V. = mitral valve.

Echocardiographic differentiation of obstructing mass in mitral orifice: Once the diagnosis of mitral stenosis has been excluded, an exploration with the echocardiograph should be undertaken in search for an obstructing mass in the mitral valve orifice. The recording of abnormal echoes from the region posterior to the anterior leaflet of the mitral valve during ventricular diastole is one of the most reliable manifestations of a tumor. However, such echoes may originate from thrombi in the left atrium or may be artifactual.[1,9]

The pendular motion of a tumor attached to the left atrial wall, produced by differences in pressure between the left atrium and left ventricle during ventricular diastole and systole, can be detected in the echocardiogram. This motion of the tumor in the heart of our patient was demonstrated beautifully at angiocardiography, and the time course of movement was also nicely followed by exploratory scanning with the echocardiograph. The illustrations reveal the tumor in position in the left atrium and then in the left ventricle.

To arrive at a reliable echocardiographic diagnosis, echoes must be obtained through at least three planes, that is, through both leaflets of the mitral valve and left ventricle, through the aorta and left atrium and through an intermediate plane displaying the anterior leaflet of the mitral valve and left atrium[10] (Fig. 2C). This latter plane is difficult to record unless the left atrium is enlarged. Occasionally, all of these planes may be recorded in one continuous rotation in direction of the beam of sound.

If a prolapsing tumor is present, an echocardiogram recorded through the first plane will reveal clouds of echoes behind the anterior leaflet of the mitral valve only during ventricular diastole (Fig. 2B). In the second plane, tumor echoes will be recorded from the left atrium only during ventricular systole (Fig. 2A). A recording from the intermediate plane will reveal tumor echoes in the left ventricle during ventricular diastole and in the left atrium during ventricular systole (Fig. 2C). These recordings provide an explanation for previous tracings considered to show the tumor in the mitral valve orifice, which rested on the anterior leaflet of the mitral valve in the left ventricle throughout the cardiac cycle.[2,11] It is therefore of utmost importance to de-

termine from which portion of the heart the echoes that are most posterior originate.

Collectively, these findings are diagnostic of a mass obstructing the mitral orifice in a ball-valve fashion and exclude the possibility that the echoes are artifacts or the results of a mass attached to the mitral valve leaflets. As indicated, the direction of the ultrasound beam is of paramount importance in determining the period of the cardiac cycle during which tumor echoes will be recorded. The appearance of an echo-free space posterior to the anterior leaflet of the mitral valve early in ventricular diastole with the appearance of abnormal echoes late during ventricular diastole is strong evidence of a tumor prolapsing through the mitral valve orifice. However, such a finding is solely dependent on the time required for the tumor to descend to the level of the ultrasound beam. Thus, in a given patient, the early echo-free space posterior to the anterior leaflet of the mitral valve during ventricular diastole will vary considerably and may therefore be a poor guide to degree of obstruction.

The characteristic configuration of the multiple mass of interrupted echo traces representing echoes from the tumor mass is important in the diagnosis of atrial myxoma. These characteristic echo lines are due to the nonhomogeneity of the tumor mass, as suggested by Effert and Domanig.[1] The motion of the tumor produces a characteristic wavy appearance of the abnormal echoes, as in those recorded from our patient and in previously reported cases.[1-6] Indeed, the lines seem to follow the motion of the normal anterior leaflet of the mitral valve and may well represent related hemodynamic phenomena. Artifacts do not have this wavy appearance, and thrombi have a characteristic dense, layered appearance.[9]

Clinical implications: This is the second case reported in which the diagnosis of left atrial myxoma was missed at routine cardiac catheterization.[6] In both instances, the patients had injection of contrast material into the left ventricle. Injection of contrast material into the pulmonary artery, with cineangiograms of the left heart, is a superior and safe method for demonstrating these tumors. Injection of contrast material directly into the left atrium using the transseptal technique[5] is not without danger.[12]

Thus, the echocardiogram is extremely useful in the diagnosis of obstructive lesions of the mitral valve orifice. Mitral stenosis and obstruction of the mitral orifice by tumor may be ruled in or out by echocardiography. The echocardiographic pattern of cor triatriatum, a lesion that may pose a problem in differential diagnosis, is distinctive.[13] The echocardiogram is most valuable when used in conjunction with history taking, physical examination, electrocardiogram and teleoroentgenograms of the chest.

The diagnosis of left atrial myxoma should be suspected in all patients with obstructive lesions of the mitral valve orifice as well as those with syncope or possible subacute bacterial endocarditis. Echocardiographic examination of such patients should be performed when feasible. Moreover, since atrial myxomas have been reported to recur,[14] periodic echocardiographic examinations should be performed in patients who have had these tumors removed. Finally, echocardiography is useful and reliable only if employed with patience, care and understanding.

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Delayed Systolic Peak of the Femoral Pulse from Kinking of the Aortic Arch

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In an asymptomatic 38 year old man, an abnormal mediastinal density was due to kinking of the aortic arch. A delay in the systolic peak of the femoral pulse compared to that of the radial pulse aided in making the correct diagnosis. Indirect pulse tracings taken simultaneously from the femoral and the right radial arteries revealed that the delayed femoral pulse was due to a longer systolic build-up time in the femoral artery than in the radial artery. The onset of the upstroke was simultaneous in both arteries as in normal persons. An aortogram demonstrated narrowing of the aortic lumen at the site of the kink. Direct intraaortic pressure measurements revealed identical peak systolic pressures in the aortic arch and in the descending aorta distal to the kink.

An abnormal superior mediastinal density on the chest roentgenogram may, on rare occasion, be due to kinking of the aortic arch. Kinking of the aortic arch has occasionally been mistaken for a mediastinal neoplasm or an aortic aneurysm and patients have been unnecessarily subjected to therapeutic irradiation or exploratory thoracotomy.[1-4] When kinking of the aortic arch coexists in a patient with a documented neoplasm or recent history of chest trauma, a confusing diagnostic problem may arise.[1,5,6] A delay in the systolic peak of the femoral pulse when compared to that of the radial pulse may elucidate this usually benign condition. This is a report of such a case.

Case Report

A 38 year old asymptomatic farmer was referred to the Minneapolis Veterans Administration Hospital because of an abnormal superior mediastinal density suggestive of an aneurysm or tumor noted on a routine chest roentgenogram (Fig. 1). There was no history of cardiac disease or chest trauma. Physical findings included a distended left external jugular vein (Fig. 2), a soft systolic ejection murmur and an ejection click along the right sternal border (Fig. 3). Palpation of the femoral pulse revealed it to be delayed when compared with the radial pulse. In addition to the mass density, the chest X-ray film also revealed a dilated ascending aorta. An aortogram revealed typical kinking of the aortic arch and a bicuspid aortic valve (Fig. 4). The left subclavian artery originated from the area of the acute kinking, and the left carotid artery originated from the aortic arch. Direct intraarterial pressure recordings taken simultaneously from the aorta proximal and distal to the area of acute angulation revealed no peak systolic pressure gradient (Fig. 5). There was no aortic regurgitation or peak systolic pressure gradient across the aortic valve.

Indirect pulse tracings taken simultaneously from the femoral and the right radial arteries revealed the simultaneous onset of the pulse upstroke in both arteries but a 120 msec delay of the systolic peak of the pulse in the femoral artery when compared to that of the radial artery (Fig. 6). Pulse recordings in 12 control subjects demonstrated that the femoral systolic peak appeared either before or simultaneously with the radial systolic peak (Table I).

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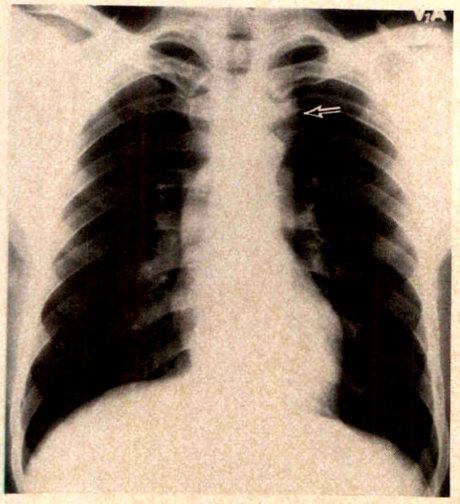

FIGURE 1. Posteroanterior chest roentgenogram revealing a well demarcated mass density in the left superior mediastinum **(arrow).** The mass density appears to be separate from the aortic arch. The ascending aorta is dilated.

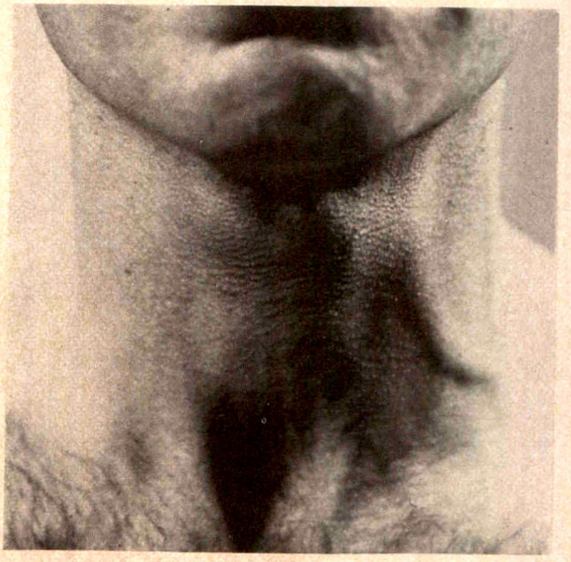

FIGURE 2. Photograph showing unilateral distension of the left jugular vein.

The patient remains asymptomatic and is currently being followed up as an outpatient.

Discussion

Kinking of the aortic arch has been recognized as a distinct roentgenographic entity[1,7] and is usually characterized by two major findings: (1) an abnormally long and redundant aortic arch, and (2) a sharp kink at the anticipated site of the attachment of the ligamentum arteriosum. The aorta proximal to the kink is elongated and rises considerably higher in the mediastinum than the normal aortic arch. The segment of aorta between the origin of the left carotid artery and the left subclavian artery is the portion of the aorta that usually contributes to the redundancy. This segment contributes to the abnormal mediastinal mass density viewed on the posteroanterior chest X-ray film. The aorta distal to the kink may be aneurysmally dilated. The acute angulation at the level of the origin of the left subclavian artery may approach 90°. In coarctation of the aorta and in senescent lengthening of the thoracic aorta, the redundant aortic segment is usually absent and the angulation is much less marked. The term pseudocoarctation has been used to refer to an abnormality of the aortic arch suggestive of either kinking of the aortic arch or mild coarctation of the aorta when no pressure gradient is measurable. This term is misleading and should be discarded.[8] This redundant aortic segment may have compressed the left innominate vein in our patient, thus leading to the unilateral distension of the left external jugular vein.

Differentiation from coarctation of aorta: Since patients with kinking of the aortic arch are usually asymptomatic, pathologic material in such cases is scant.[9-12] Coarctation of the aorta is characterized by an internal ridge composed of aortic media occurring at a point opposite the ductus arteriosus or the

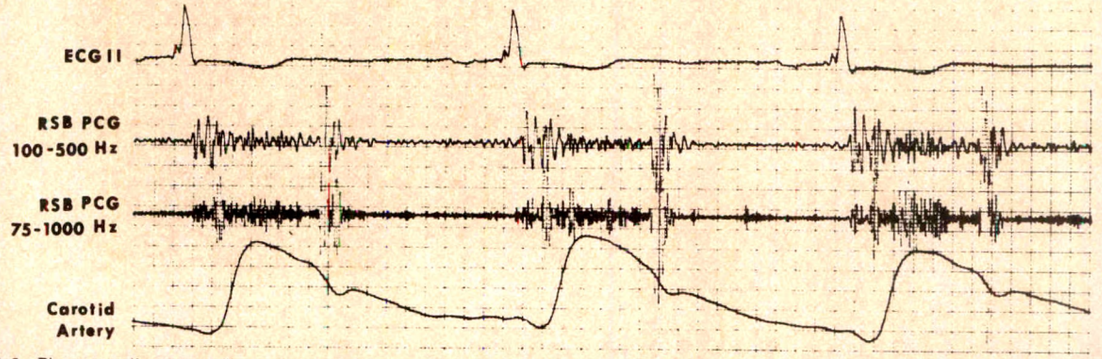

FIGURE 3. Phonocardiogram taken at the right second intercostal space simultaneously with electrocardiographic lead II and carotid arterial pulse tracing. A systolic ejection click is followed by a systolic ejection murmur. The tracing was obtained using a Mingograf 34 direct writing recorder with ink jet galvonometers and a frequency response linear from 0 to 500 Hz. RSB PCG = right sternal border phonocardiogram.

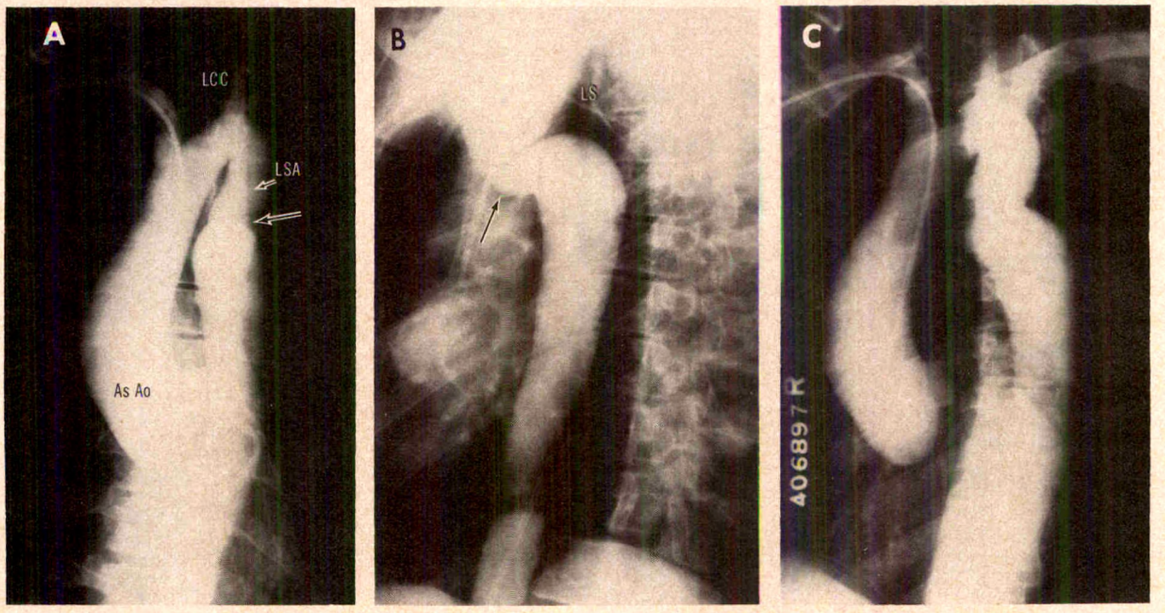

FIGURE 4. Aortograms **A,** taken in the anteroposterior projection. Contrast material was injected into the ascending aorta (AsAo) through a catheter introduced from the right brachial artery. The aortogram demonstrates two aortic valvular cusps and a dilated ascending aorta. The kinked portion of the aorta is indicated by the **lower arrow.** The aorta proximal to the kink is elongated and rises high in the superior mediastinum. The distance from the left common carotid (LCC) artery to the left subclavian artery (LSA) is lengthened. **B,** taken in the steep left anterior oblique projection with the catheter positioned as in **A.** This view demonstrates the kinking at the anticipated site of the ligamentum arteriosum **(arrow).** The left subclavian (LS) artery also arises from the same area. This projection reveals narrowing of the aorta at the site of the kink. There is a moderate degree of aneurysmal dilation of the aorta distal to the kink. **C,** taken 30° in the left anterior oblique projection with the catheter in the same position as in **A** and **B.** The bicuspid nature of the aortic valve is best seen in this view.

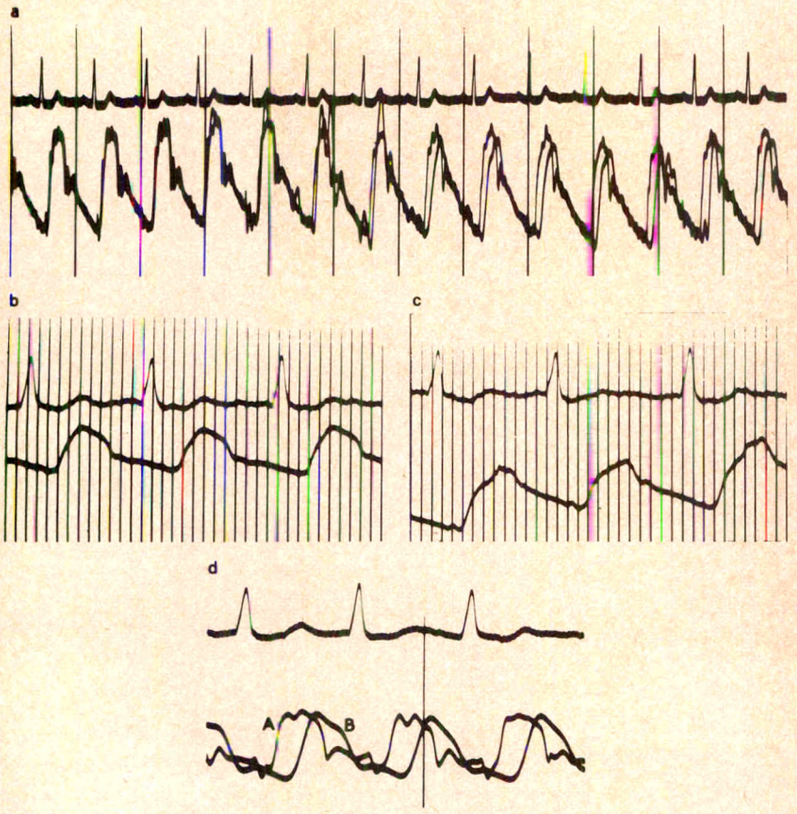

FIGURE 5. Pressure tracings. **a,** intraaortic, recorded from two Teflon® catheters during withdrawal of one catheter from the ascending aorta to a point distal to the kinked segment. The second catheter remained in the ascending aorta. Note the lack of appreciable pressure gradient across the site of kinking. **b,** tracing in the ascending aorta from a catheter-tip transducer. The patient had atrial fibrillation during this and subsequent recordings. **c,** tracing taken in abdominal aorta from the same catheter-tip transducer used in **b.** The systolic upstroke is prolonged compared to that in **b. d,** simultaneous intraaortic pressure tracings taken from two Teflon catheters, one in the ascending aorta (A) and the other in the midabdominal aorta (B). The build-up time is prolonged, and the systolic peak is delayed in the abdominal aorta when compared to that of the ascending aorta.

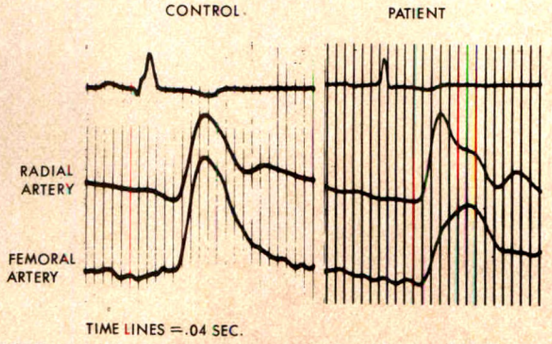

FIGURE 6. Indirect pulse tracings and electrocardiogram taken simultaneously from the right radial artery and the right femoral artery. In a representative normal subject **(left)**, the onset of the systolic upstroke and the systolic peak are simultaneous in both arteries. In contrast, the patient **(right)** has a 120 msec delay of the systolic peak of the femoral artery compared to the radial artery, whereas the onset of the upstroke is simultaneous in both arteries. Pulse tracings were obtained from an Electronics for Medicine, Inc. PS-2 ceramic microphone with a time constant of 1.2 seconds in the pulse position.

ligamentum arteriosum.[12] This internal ridge may or may not be obstructive. Clinical, roentgenographic and hemodynamic findings are dependent upon the degree of obstruction by this internal ridge. Consequently, some observers, finding anatomic evidence of an internal ridge in patients with roentgenographic findings of kinking of the aortic arch, conclude that these cases represent a variation of mild coarctation of the aorta.[10,12] Other observers have failed to document such an internal ridge in patients with kinking of the aortic arch.[9] Further elucidation of this problem awaits additional anatomic observation in patients with X-ray findings characteristic of kinking of the aortic arch. In the interim it seems reasonable to distinguish patients with such X-ray findings from those with typical coarctation, recognizing that they may have only a variant of mild anatomic coarctation of the aorta. We have outlined these differences in Table II. A bicuspid aortic valve, ventricular septal defect, atrial septal defect and patent ductus arteriosus all have been found in patients with X-ray findings typical of kinking of aortic arch.[2,9,11] This association of congenital anomalies lends support to the concept that coarctation of the aorta and kinking of the aortic arch may have a similar pathogenesis.[12]

Femoral pulse tracing as diagnostic aid: A delay in the femoral pulse when compared to the radial pulse has been a useful aid in diagnosing kinking of the aortic arch,[13,14] although some investigators have noted no such delay.[15] Indirect pulse tracings taken simultaneously from the right radial artery and the right femoral artery in our patient revealed that the clinically detected delayed femoral pulse is due to a prolonged build-up time resulting in a delayed systolic peak. As in normal persons, the onset of the upstroke in both the radial and femoral arterial pulses was simultaneous.[16,17] This finding

TABLE I

Comparison of Systolic Upstroke and Peak in Indirect Radial and Femoral Arterial Pulses (mean values in 12 control subjects)

	Q to Onset of Upstroke*		Q to Systolic Peak	
Time (msec)	Radial	Femoral	Radial	Femoral
Mean	187.5	185.4	298.3	296.3
Standard deviation	±13.6	±12.9	±21.6	±18.5
Range	(165–210)	(165–200)	(275–330)	(270–325)
Probability (*P*) value	>0.3		>0.5	

* Timed from Q wave of electrocardiographic lead II.

TABLE II

Comparison of Kinking of Aortic Arch and Coarctation of Aorta

		Coarctation of Aorta	
	Kinking of Aortic Arch	Subclinical[18] (mild)	Clinical (severe)
Kinking or buckling	+	−	−
High aortic arch	+	−	−
Distance between left common carotid artery and left subclavian artery	Long	Normal	Normal
Localized constriction with internal ridge	−[9] or +[10,12]	+	+
Pressure gradient	Usually −	−	+
Collateral circulation	−	−	+
Rib notching	−	−	+
Occasional association with a bicuspid aortic valve	+	+	+

\+ = present, − = absent.

suggests that there is some narrowing of the aortic lumen at the site of kinking. In experimental animals with a progressively constricted aorta, the delayed systolic peak in the distal aorta preceded the appearance of the peak systolic pressure gradient.[18] In that experiment, the contour of the distal aortic pulse wave began to change when the aorta was constricted to 40 percent of its original external cross-sectional area whereas the reduction in systolic pressure in the distal aorta did not occur until the aorta was constricted to less than 35 percent of its original cross-sectional area.[18]

These experimental data indicate that the differentiation between coarctation and kinking of the aorta cannot be based on mere demonstration of presence or absence of a peak systolic pressure gradient across the aortic lesion.[19] Coarctation of the

aorta may not produce a peak systolic pressure gradient so long as the constriction is mild; and, kinking of the aortic arch has been associated with peak systolic pressure gradient when the aortic lumen was significantly compromised by the kinking.[14,15] Presence or absence of a peak systolic pressure gradient, collateral circulation, rib notching, proximal hypertension and left ventricular hypertrophy reflect only the degree of constriction and not the underlying pathologic features. On the other hand, kinking of the thoracic aorta alone, by disturbing the relation of incident and reflected pressure waves, may reduce the normal systolic amplification, thereby leading to a prolonged build-up time in the distal aorta (Fig. 5).[16,17]

Embryology: One current view of the embryology of kinking of the aortic arch indicates that failure of the normal "compression" of the left fourth aortic arch and third to seventh dorsal aortic root segments during development results in an abnormally long aortic arch that kinks at the fixed point, namely, the insertion of the ligamentum arteriosum.[1] Failure of "compression" of the left fourth aortic arch may account for the abnormally long distance between the origins of the left common carotid artery and the left subclavian artery characteristic of this condition. On the other hand, the fact that the origin of the left subclavian artery in this condition is not in the midthoracic aorta but either proximal to or at the level of the ligamentum arteriosum, as in normal persons, does not make it likely that there was failure of the compression of the third to seventh dorsal aortic root segment. It also seems reasonable that the elongated segment of aorta could be formed by the third arch and a persistent left carotid duct.[3]

Clinical implication: Recognition of kinking of the aortic arch can avoid unnecessary irradiation or an exploratory thoracotomy. Although this condition is generally considered to be benign and to require no treatment, this may not always be true. Gay and Young[20] reported a fatal case in which the aorta distal to the kinking became aneurysmal and ruptured. Three other patients had timely and successful resection of aneurysms with graft replacement and are doing well 1 to 8 years after operation. It has also been advised[11] that patients with this condition should be protected from bacterial endocarditis or endarteritis because of the possibility of infection at the site of the kink or in the associated aortic valvular or other cardiac anomalies.

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Demonstration of Dual Atrioventricular Nodal Pathways in Man

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Electrophysiologic studies in a patient manifesting two P–R intervals revealed two ranges of atrioventricular (A–V) nodal conduction time (A–H intervals) and two A–V nodal effective and functional refractory periods. Similar demonstrations in patients with paroxysmal supraventricular tachycardia would strongly support the presence of longitudinal A–V nodal dissociation with reentry as a causative mechanism.

Recent studies suggest that atrioventricular (A–V) nodal reentry is a mechanism of paroxysmal supraventricular tachycardia in man.[1–3] The demonstration of A–V nodal reentry implies, but does not prove, the existence of functional dissociation of the A–V node into two pathways, one utilized for anterograde and the other for retrograde conduction.[4,5]

The direct demonstration of dual A–V nodal pathways is dependent upon evidence of dual A–V nodal conduction times and refractory periods. Mendez et al.[6] provided such evidence in dogs, utilizing premature His bundle stimulation. At critical coupling intervals, they noted sudden prolongation of retrograde A–V nodal conduction times (from His bundle to low atrium) with simultaneous occurrence of ventricular echoes. This suggested block in a fast A–V nodal pathway with conduction from the His bundle to the atria proceeding by way of a slow A–V nodal pathway. The impulse could return to the ventricles over the previously failed fast pathway. The critical coupling interval at which sudden prolongation occurred would be the effective refractory period of the fast pathway. Subsequent microelectrode studies in rabbit hearts by Mendez and Moe[7] suggested that functional dissociation into dual pathways occurred in the upper part of the A–V node.

The only previous experimental demonstration of a similar phenomenon in man has been indirect. Schuilenburg and Durrer,[8] using coupled ventricular stimulation in patients, demonstrated sudden prolongations of retrograde conduction time (from ventricles to atrium) with simultaneous occurrence of ventricular echoes at critical coupling intervals. Since His bundle electrograms were not recorded in their study, the exact sites of retrograde conduction delay could not be delineated.

The catheter recording of His bundle electrograms should allow demonstration of dual A–V nodal pathways, if these occur in man.[9] We recently performed such recordings in a child who, after repair of a ventricular septal defect, intermittently manifested two P–R intervals, one of 0.18 second and the other of 0.42 second. The changes from one P–R interval to the other were sporadic and unpredictable.

Electrophysiologic Study

The A–H interval, a measure of A–V nodal conduction time,[10] was 90 msec during spontaneous sinus rhythm (Fig. 1A). At an atrial paced rate of 90/min, two A–H intervals were recorded, one of 100

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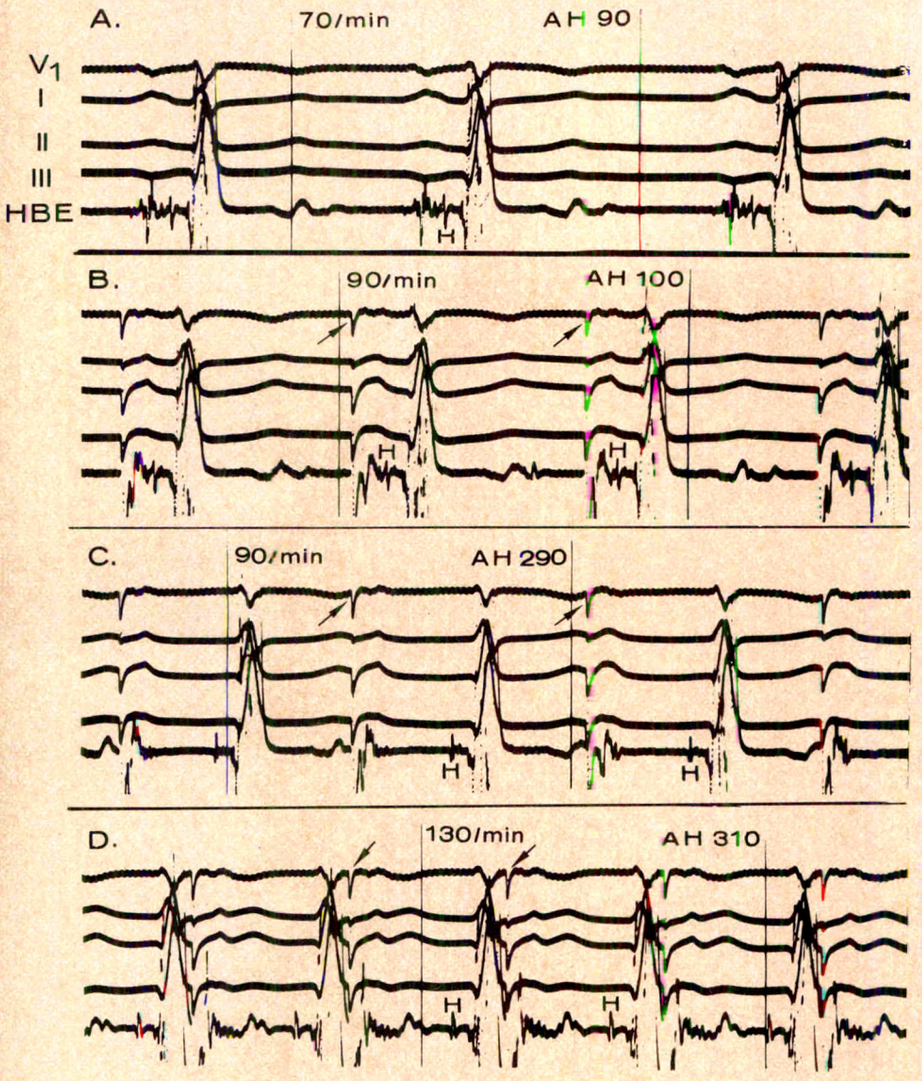

FIGURE 1. Demonstration of dual A–V nodal conduction times. Shown are electrocardiographic leads V_1, I, II and III and His bundle electrogram (HBE). Paper speed is 100 mm/sec and times lines are at 1 second intervals. His bundle potentials are labeled H. **A,** sinus rhythm with an A–H interval of 90 msec (fast pathway). **B,** atrial pacing at 90/min (pacing impulses labeled with **arrows**). The fast pathway is being utilized (A–H interval 100 msec). **C,** atrial pacing at 90/min. The slow pathway is being utilized (A–H interval 290 msec). **D,** atrial pacing at 130/min with conduction over the slow pathway (A–H interval 310 msec).

msec and the other of 290 msec (Fig. 1, B and C). The transition between shorter and longer A–H intervals was abrupt, with series of short A–H intervals being followed by series of long A–H intervals at identical cycle lengths. Series of long A–H intervals also changed abruptly to series of short A–H intervals. Each pathway maintained itself for various periods of time (up to 5 minutes). At paced rates above 100/min, A–H intervals were between 300 and 380 msec (Fig. 1D). Wenckebach periods proximal to the His bundle were noted at a paced rate of 145/min. The QRS configuration and H–V intervals were constant despite changes in the A–H interval.

Refractory periods were measured with an atrial extrastimulus introduced following every 10th sinus beat (Fig. 2).[11] The extrastimuli (A_2) were coupled to the atrial electrogram of the spontaneous beat (A_1) and were given progressively earlier (in 10 msec steps). The response to several extrastimuli was tested at each coupling interval. H_1 was the His bundle electrogram of the last sinus beat before the extrastimulus and H_2 was the His bundle electrogram of the coupled beat. The impulse was propagated along the fast pathway with A_1–H_1 intervals remaining between 90 and 100 msec during this portion of the study. Sinus rhythm was regular, allowing reproducible recordings.

The H_1–H_2 responses were plotted against the A_1–A_2 coupling intervals (Fig. 2 and 3). As the A_1–A_2 interval was shortened from 600 to 530 msec, the H_1–H_2 interval shortened from 600 to 565 msec (Fig. 2A). At an A_1–A_2 interval of 520 msec, one of two H_1–H_2 responses was noted, either fast (570 msec) or slow (715 msec) (Fig. 2, B and C). Similar fast or slow responses were noted at A_1–A_2 intervals of 520 to 460 msec (Fig. 2, D and E). At A_1–A_2 intervals of 450 msec or less, only slow responses were seen (Fig. 2, F and G). The limiting factor for A–V con-

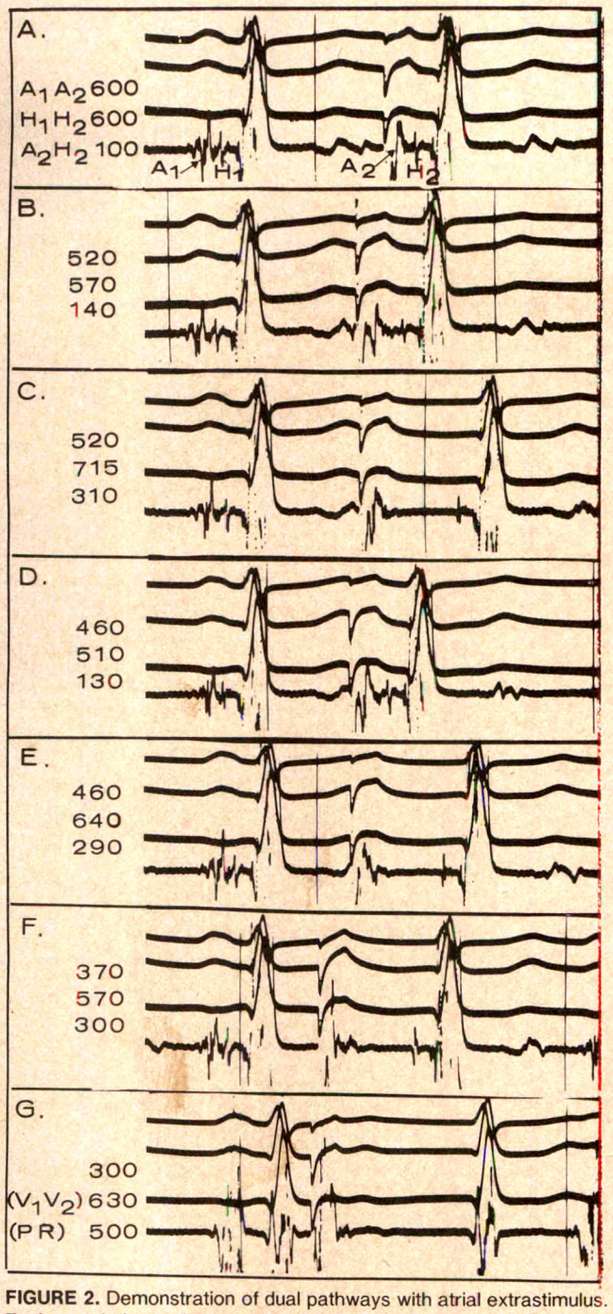

FIGURE 2. Demonstration of dual pathways with atrial extrastimulus. Each panel shows the last sinus beat before the extrastimulus. A_1, H_1, A_2 and H_2 are labeled in the upper panel. A_1–A_2, H_1–H_2 and A_2–H_2 are listed for each panel on the left. **A, B** and **D** show fast responses; **C, E, F** and **G** show slow responses. The His bundle electrogram was transiently lost toward the end of the procedure **(G),** so that leads V_1 and V_2 and the P–R interval are listed in that panel. See text for discussion.

duction was the atrial effective refractory period of 290 msec.

Examination of the graph (Fig. 3) suggested two A–V nodal refractory periods. The effective refractory period of the fast pathway was the longest A_1–A_2 interval at which A_2 failed to conduct to the His bundle by way of the fast pathway and ranged between 450 and 520 msec. The functional refractory period of the fast pathway was the shortest H_1–H_2 interval achieved utilizing this pathway and was 510 msec. Similar determinations for the slow pathway revealed an effective refractory period of less than 300 msec and a functional refractory period of 560 msec. Studies of the extrastimulus response after administration of atropine were incomplete but suggested that both fast and slow curves were shifted downward and to the left.

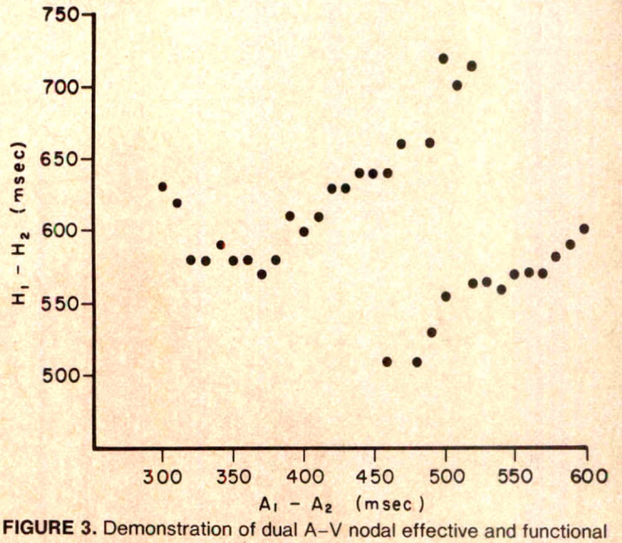

FIGURE 3. Demonstration of dual A–V nodal effective and functional refractory periods. A_1–A_2 coupling intervals are plotted on the **abscissa;** H_1–H_2 responses are plotted on the **ordinate.** Note the striking discontinuity in the fast pathway curve **(lower right)** and the slow pathway curve **(upper left).** At coupling intervals of 450 msec or less, only the slow pathway is utilized.

Discussion

The demonstration of two ranges of A–H intervals as well as dual A–V nodal effective and functional refractory periods suggests the presence of dual A–V nodal pathways. These could reflect a functional A–V nodal dissociation or an anatomic discontinuity in the node secondary to previous surgery. The possibility that the fast pathway is an accessory pathway[12] entering the distal node or His bundle is unlikely since the A–H interval of 90 msec does not suggest A–V nodal bypass. Both slow and fast pathways appeared to be under control of the parasympathetic nervous system.

The absence of echoes with premature stimulation may reflect retrograde refractoriness of the fast pathway. Despite the absence of echoes, the demonstration of dual A–V nodal pathways is relevant to paroxysmal supraventricular tachycardia in man. If similar A_1–A_2, H_1–H_2 curves could be demonstrated in patients with paroxysmal supraventricular tachycardia, this finding would strongly support the presence of longitudinal A–V nodal dissociation with reentry as a causative mechanism of the arrhythmia.

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Pacemaker-Induced Cardiovascular Failure

Hemodynamic and Angiographic Observations

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A 71 year old woman underwent permanent transvenous right ventricular pacemaker implantation for prolonged syncope and atrioventricular conduction defects. Each time the patient's heart rate spontaneously decreased to less than 70 beats/min, cardiovascular collapse with hypotension and reduced cardiac output occurred. Left ventricular cineangiography performed during both sinus rhythm and right ventricular pacing demonstrated reduced left ventricular end-diastolic volume, secondary to a loss of atrial contribution to left ventricular filling, and severe, acute mitral regurgitation with significantly decreased effective stroke volume and cardiac output. Pacing from the left ventricular endocardium had the same effect. The detrimental effects of cardiac pacing necessitated removal of the right ventricular pacemaker.

Since the introduction of artificial cardiac pacemakers the prognosis of patients with conduction disturbances and complete heart block has been improved. Nevertheless, the literature is replete with reports on problems associated with pacemaker implantation. Pulse-generator failure, infections at the site of generator implantation, malposition or dislocation of the endocardial electrode catheter, perforations of the septal and free right ventricular wall, arrhythmias, thrombus formation and pulmonary emboli represent the vast majority of complications in our experience and in several large series reported by others.[1–3] These reports have not mentioned the need to discontinue asynchronous ventricular pacing because of significant deleterious hemodynamic effects on cardiac output.

The loss of atrial contribution to ventricular filling and stroke volume has been studied, and the hemodynamic consequences of nonsequential atrioventricular output has been emphasized by Samet et al.[4] The deleterious effect of mitral insufficiency has been cited as a relative indication for atrial synchronous pacing by Furman and Escher.[5] In this report we document hemodynamically and cineangiographically similar complications requiring discontinuation of asynchronous right ventricular endocardial pacing.

Methods

Atrial pacing was accomplished with a Cordis temporary pervenous bipolar no. 4F pacing catheter and a Medtronic pulse generator (model 5837). Percutaneous retrograde right and left heart catheterization was performed, with pressures recorded using Statham P23DB transducers and an 8-channel Hewlett-Packard recorder. Left ventricular cineangiograms were obtained on 16 mm film at 30 frames/sec, using meglumine diatrizoate (Renografin-76®) as the contrast medium. Left ventricular volume was calculated according to the method of Sandler and Dodge[6] from the single plane cineangiogram obtained in the right anterior oblique projection and corrected with the regression equation of Kennedy et al.[7] Cardiac output was determined by the Fick method, with blood gas and air analysis performed on IL co-oximeter instru-

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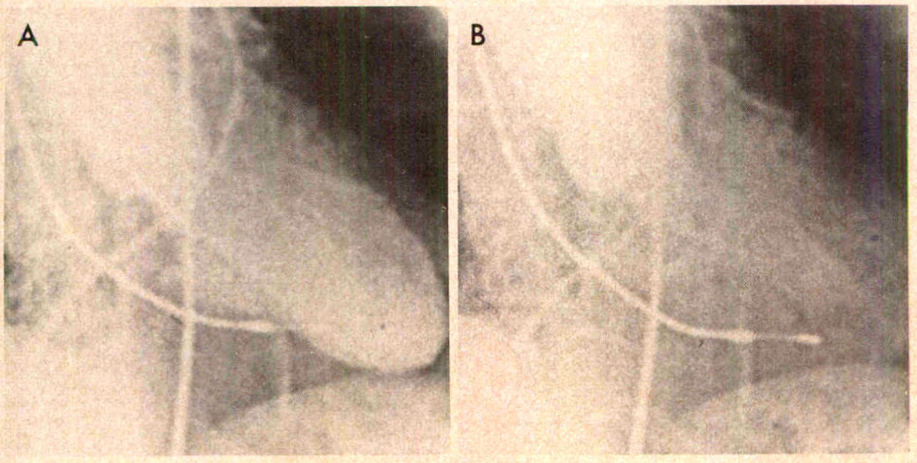

FIGURE 1. Left ventricular cineangiography during normal sinus rhythm. **A**, demonstrating left ventricular end-diastolic volume. **B**, demonstrating left ventricular end-systolic volume and absence of any mitral regurgitation.

ments (models 113 and 182). Right ventricular pacing during cardiac catheterization was accomplished with a bipolar endocardial catheter and a General Electric implantable ventricular inhibited standby pulse generator (model A2072D). Left ventricular pacing was performed using a no. 7F bipolar Zucker catheter to obtain simultaneous left ventricular pressures.

Case Presentation

The patient, a 71 year old white woman, had a significant history of several transient bouts of syncope the year before admission. Her current hospitalization was precipitated in October 1972 by a prolonged syncopal episode at home. En route to the hospital, the ambulance attendant noted a radial pulse of 30/min and no obtainable blood pressure. On arrival at the emergency room, the patient gradually regained consciousness, and an electrocardiogram disclosed normal sinus rhythm with a rate of 60/min; blood pressure was 200/70 mm Hg. History indicated possible previous angina pectoris but no definite documented myocardial infarction. The patient currently experienced shortness of breath and dyspnea on exertion but had no definite history of frank congestive heart failure. She had been treated previously with methyldopa and Dyazide® for hypertension.

Physical examination showed an elderly, alert and oriented white woman with a heart rate of 68 beats/min and blood pressure of 190/88 mm Hg. There was slight arteriovenous nicking on funduscopic examination. Jugular venous pulse and pressure were normal. The lungs were clear to auscultation and percussion. There was no hepatosplenomegaly or edema. Peripheral pulses were intact and full. Results of a neurologic examination were normal. Examination of the heart revealed normal sinus rhythm. The apical impulse was in the fifth intercostal space at the midclavicular line with a slight left ventricular impulse. A grade 2–3/6 systolic ejection murmur heard over the aortic outflow tract radiated to the carotid arteries. No gallop sounds were noted.

The electrocardiogram showed left ventricular hypertrophy by voltage criteria with slight sagging of the S–T segments. Chest X-ray films revealed slight cardiac enlargement with prominence and calcification of the aortic arch.

The patient was observed for 24 hours with an Avionics Holter monitor which revealed no arrhythmias or conduction disturbances. Diagnostic atrial pacing was performed. First degree atrioventricular (A–V) block occurred at a rate of 100/min and 2:1 A–V block as the rate was increased to 125/min. Sinus nodal recovery time was normal after abrupt discontinuation of atrial pacing. On November 15, a General Electric implantable ventricular inhibited standby pulse generator (model A2072D) with a bipolar endocardial electrode was inserted with use of 1 percent Xylocaine® and Valium®-induced anesthesia. Good ventricular capture was obtained at 0.5 milliamperes. During pacemaker testing, there was a transient reduction in blood pressure from 200/80 to 160–180/60 mm Hg. The patient was returned to the recovery room in satisfactory condition.

Postoperatively the patient's blood pressure during normal sinus rhythm was 180–190/80–90 mm Hg. On several occasions during the night, her inherent sinus rhythm fell below the pacemaker rate of 70/min and during effective artificial pacing the blood pressure level fell to 70–80/40–50

TABLE I

Cardiac Catheterization Data

	Normal Sinus Rhythm	Right Ventricular Pacing
Heart rate (beats/min)	72	70
Pressures (mm Hg)		
Right atrium	9/5 (6.5)	...
Right ventricle	29/0–3	...
Pulmonary artery	27/10 (15)	...
Pulmonary artery wedge	18/6.5 (12)	(20)
Systemic artery	183/60 (110)	86/30 (53)
Left ventricle	188/0–13	81/0–8
Volumes (cc)	168/0–8	70/0–8*
Left ventricular end-diastolic	86	65.6
Left ventricular end-systolic	14.5	12.9
Systolic ejection fraction (%)	83.5	81
Stroke volume	71.8	53
Effective stroke volume	71.8	37
Cardiac output (Fick) (liters/min)	5.17	2.67
Cardiac index (Fick) (liters/min per m^2)	3.38	1.75

* Left ventricular pacing.
Figures in parentheses indicate mean values.

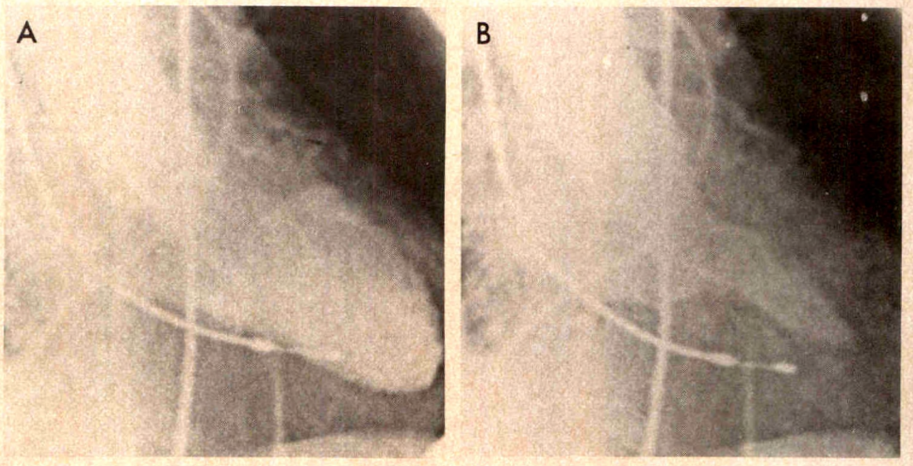

FIGURE 2. Left ventricular cineangiography during right ventricular endocardial pacing. **A,** demonstrating left ventricular end-diastolic volume. **B,** demonstrating left ventricular end-systolic volume and opacification of the left atrium consistent with significant mitral regurgitation.

mm Hg. During this time physical examination revealed mental obtundation and a small pulse pressure; the heart sounds became distant and the previously described aortic systolic ejection murmur disappeared. Mitral insufficiency could not be definitely heard at the bedside. The patient was treated with intravenously administered atropine and, with a return to normal sinus rhythm, the blood pressure quickly increased to 190/90 mm Hg and the mental condition cleared. On November 16, percutaneous right and retrograde left heart catheterization was performed (Table I).

Comment: Acute cardiovascular deterioration occurred repeatedly whenever the patient's inherent sinus rhythm fell below the preset right ventricular artificial pacemaker rate of 70/min, either spontaneously or by induction through carotid massage. Hemodynamic studies with left ventricular cineangiography were performed to determine whether this sequence of events resulted from a loss of atrial contribution to left ventricular filling, acute mitral regurgitation or ventricular asynchrony with impairment of left ventricular function. The results revealed a 23 percent reduction in left ventricular end-diastolic volume associated with a decrease of 5 mm Hg in left ventricular end-diastolic pressure during asynchronous right ventricular pacing compared to values during normal sinus rhythm, indicating a significant loss of atrial contribution to left ventricular filling.

No mitral regurgitation was noted during sinus rhythm, but it developed during right ventricular pacing. As a result, effective stroke volume was reduced by 30 percent to 37 cc, with an overall reduction in the cardiac index from

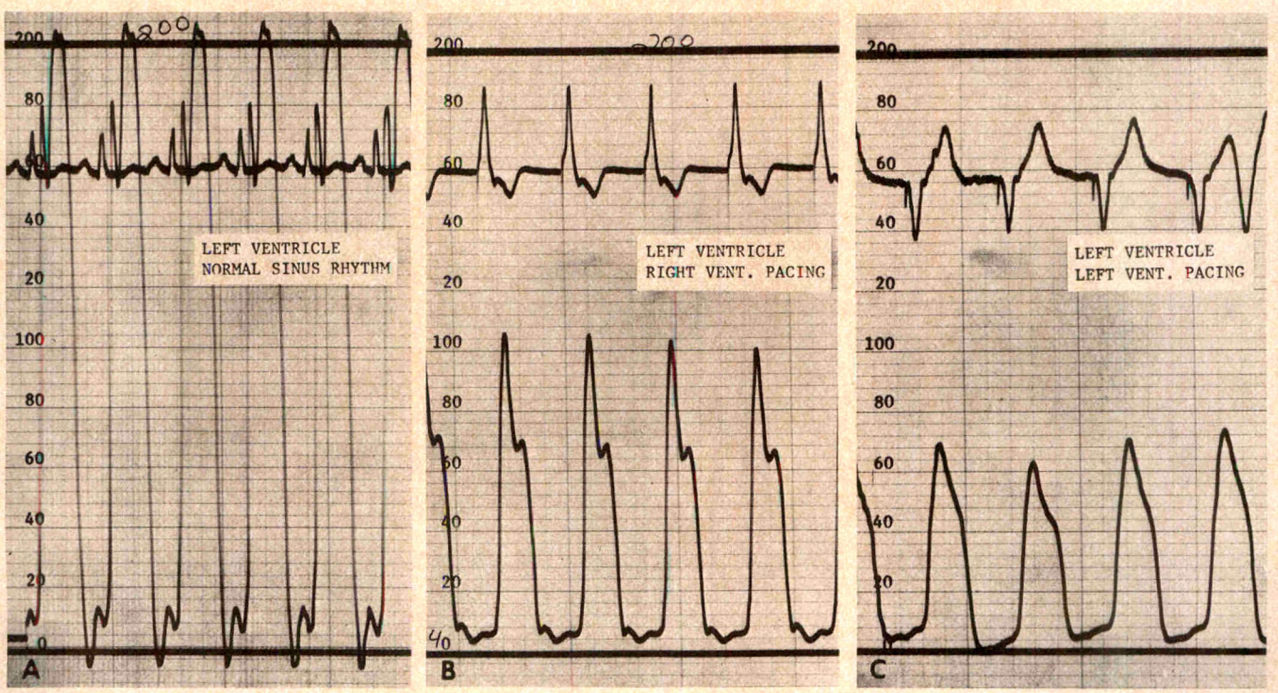

FIGURE 3. Left ventricular pressure curve. **A,** recorded during normal sinus rhythm. **B,** recorded during right ventricular endocardial pacing. **C,** recorded during pacing from the apex of the left ventricle.

3.38 to 1.75 liters/min per m^2. There was no asynchrony or dyskinesis of left ventricular contraction, and contractility and the systolic ejection fraction remained unchanged during right ventricular pacing from cineangiographic data obtained during normal sinus rhythm (Fig. 1 and 2). Pacing from the left ventricle showed the same deterioration in left ventricular and systemic pressures that occurred with right ventricular pacing (Fig. 3) and although left ventricular cineangiography was not performed, one must assume that the same phenomena with loss of atrial contribution to left ventricular filling and mitral regurgitation occurred.

The transvenous right ventricular endocardial pacemaker was removed. The patient refused thoracotomy and implantation of a synchronous atrioventricular pacemaker.

Discussion

Ventricular asynchrony, loss of atrial contribution to ventricular filling, and the deleterious effects of A–V valvular incompetence have all been mentioned as causes of ventricular dysfunction and reduced cardiac output with asynchronous ventricular pacing. The optimal site for ventricular pacing has also been studied in an effort to explain hemodynamic alterations with asynchronous pacing.

Role of ventricular asynchrony: There are conflicting reports concerning the role of ventricular asynchrony as a determinant of ventricular function. Several investigators[8–10] have presented evidence that cardiac performance does not vary with ventricular pacemaker site. Barold et al.[11] found no significant difference between endocardial pacing from the inflow and outflow tracts of the right ventricle. Lister et al.[12] and Finney[13] indicated that the left ventricular apex is the most favorable pacemaker site in relation to left ventricular function. Aberrant ventricular depolarization with alteration in papillary muscle function has been invoked as a probable cause of left ventricular asynchrony and A–V valvular insufficiency. In our patient, pacing from the apex of the right ventricular endocardium and from the apex of the left ventricular endocardium produced the same degree of cardiovascular deterioration and myocardial failure.

Role of loss of atrial contribution to ventricular filling: Our observations most closely resemble those of Samet et al.,[14,15] who demonstrated that the primary reason for the hemodynamic differences between atrial and ventricular pacing is the absence of synchronized atrioventricular activity during ventricular pacing. They concluded that aberrant ventricular depolarization in itself resulted in little decrease in cardiac indexes and showed that the hemodynamic sequelae of ventricular pacing were secondary to a significant loss of atrial contribution to ventricular filling. A consistent reduction in left ventricular end-diastolic pressure was thought to reflect a decrease in left ventricular volume. A similar sequence of events could be demonstrated during atrial fibrillation and during short bursts of ventricular extrasystoles. They demonstrated an increase in left atrial pressure when the P wave occurred slightly after or simultaneously with the QRS complex with ventricularization of the left atrial pressure curve suggesting regurgitation. The various degrees of A–V insufficiency caused by asynchronous pacing have been emphasized by Furman and Escher.[5] Mitchell et al.[16] noted a 19 percent reduction in ventricular stroke volume when ventricular contraction was not preceded by atrial systole. A 15 percent increment in cardiac output when atrial systole preceded ventricular activity was also noted by Sellers et al.[17] Samet et al.[14] demonstrated that cardiac output in patients with complete heart block studied during synchronous atrioventricular pacing increased 15 to 20 percent from values obtained during right ventricular catheter outflow tract pacing.

The findings in our case argue against ventricular asynchrony dyskinesis or impairment of ventricular contractility as a mechanism. They support the observations of others that a significant loss of atrial contribution to ventricular filling (approximating 23 percent) and significant mitral insufficiency (approximating 30 percent of stroke volume) is the cause of the cardiovascular deterioration.

The pacemaker syndrome resulting from asynchronous ventricular pacing has been long recognized to occur in various lesser degrees. Although we have not previously encountered a case similar to ours, we believe that the syndrome should be considered in any patient whose condition for unexplained reasons does not improve or deteriorates with ventricular pacing. Our observations favor performing synchronous atrioventricular pacing from the right atrium or coronary sinus whenever possible.

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Double Opening Sound Related to Dysfunction in a Caged Disc Mitral Valve Prosthesis

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A grooved embolic fragment was removed from the femoral artery of a patient with a Kay-Shiley caged disc mitral valve prosthesis. An extra opening click that had been present before embolization disappeared coincidentally. This study demonstrates (1) the importance of establishing an expected range of normal systolic time intervals for a given prosthetic heart valve configuration, (2) the value of postoperative phonocardiograms in documenting the presence of an unexpected extra sound, and (3) the need for careful examination of embolic fragments recovered from patients with valve prostheses.

Approximately 40 different prosthetic heart valves are now commercially available in the United States.[1] Of these, approximately 10 are of the caged disc design used primarily for mitral valve replacement. Caged disc prostheses have been used clinically for about 10 years, but the normal opening and closing time intervals and the quality of valve sounds have been established for only a few of the prostheses in general use. Although each valve prosthesis may possess a distinct but typical acoustic signature arising from a particular combination of mechanical design features and materials of construction, these signatures may become modified postoperatively by alterations of blood flow and heart motion and by various pathologic conditions.

In cases of severe dysfunction the sounds of prosthetic disc valves may be significantly altered and are detected easily.[2–7] In other cases of valvular dysfunction the sounds may remain essentially normal.[8–10]

The case presented here demonstrates how meticulous clinical follow-up studies, which included serial phonocardiographic recordings, were used to detect the presence and clarify the origin of the double opening click of a caged disc mitral valve prosthesis. The significance of the double opening click, which we had not encountered previously, is discussed.

Case Report

A 39 year old housewife underwent mitral valve replacement in February 1967 for severe mitral regurgitation of rheumatic origin; there was no evidence of aortic valve disease. A size 8, series K, Kay-Shiley caged-disc mitral valve was implanted; this prosthesis model is no longer in commercial production. The patient's functional status improved from New York Heart Association class 4 to class 2 in spite of persistent atrial fibrillation. She was examined in the clinic every 4 weeks and phonocardiographic recordings were obtained periodically with a Siemens-Elema Mingograf recorder. Her medications included digoxin, 0.25 mg daily, hydrochlorothiazide, 50 mg daily, potassium supplement, and warfarin sodium to maintain prothrombin activity at less than 20 percent. In October 1970 (44 months postoperatively) a double opening click of the mitral prosthesis was first noted (Fig. 1, top). However, no murmur could be detected, and functional status had not altered. Although the double opening click was detected on subsequent visits, the patient refused further investigation.

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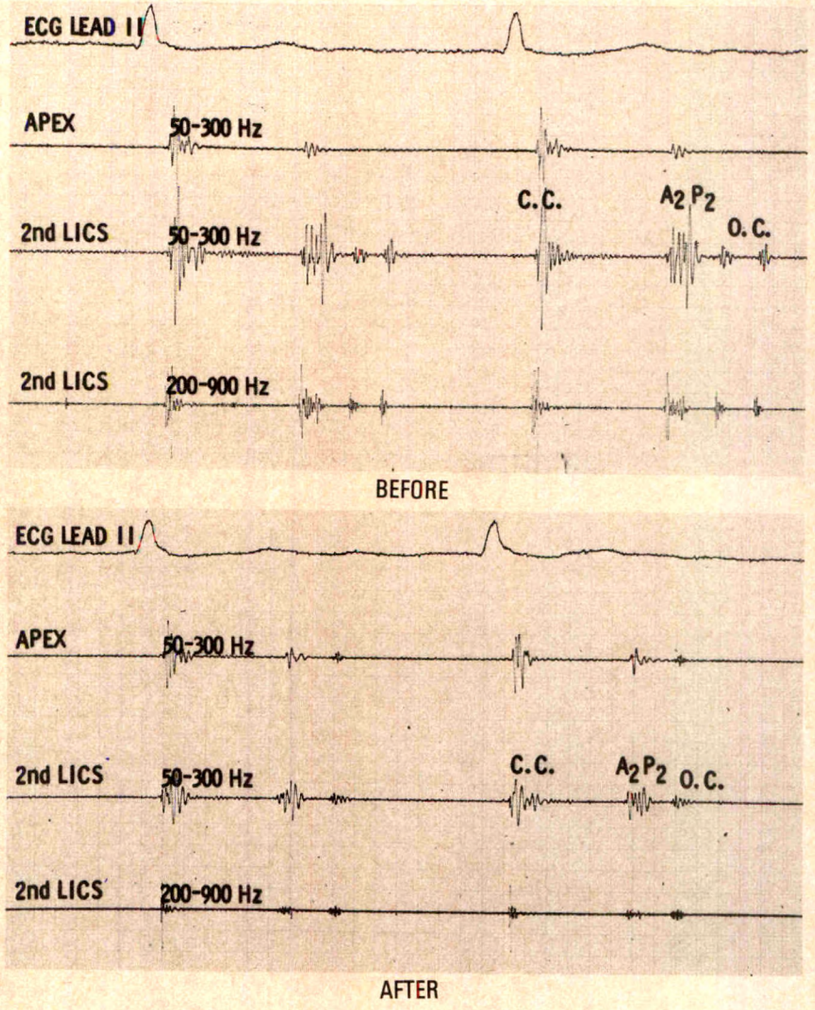

FIGURE 1. Phonocardiograms before **(top)** and after **(bottom)** embolic occlusion of the patient's left femoral artery. Note the disappearance of the second opening click of the mitral prosthesis after dislodgment of the thrombus fragment believed to have formed originally on a cage strut of the valve **(bottom).** A_2 and P_2 = closing sounds of the aortic and pulmonary valves, respectively; C.C. and O.C. = closing and opening clicks, respectively, of the mitral prosthetic Kay-Shiley disc valve. Each large time division is equivalent to 50 msec.

In August 1971 she was admitted to the hospital with a cold, pulseless left lower limb. The double opening click had disappeared (Fig. 1, bottom). An elongated embolic fragment removed from the patient's left femoral artery had an unusual groove along its entire length (Fig. 2, right). The embolic fragment was found to mate closely with the cage strut of a new prosthetic valve of the same size and model as that implanted 54 months earlier (Fig. 2, left). Additional thrombus was suspected to exist on the cage of the valve prosthesis; however, the patient refused to consider valve replacement. Subsequently she was discharged from the hospital with normal pulses in her left lower limb. She was readmitted in June 1972 in a comatose condition with flaccid right limbs and died the following day. The family refused autopsy.

Discussion

Results of previous studies on acoustic changes in prosthetic mitral disc valves[2–11] are summarized in Table I. Principal modes of dysfunction include (1) restricted motion or jamming of the disc due to obstruction by fibrinous tissue or thrombus on valve elements, (2) notching or uneven wear of the disc leading to eventual jamming, (3) disc cocking caused by uncorrected aortic regurgitation, and (4) valve detachment caused by suture disruption. Dysfunction can occur in nearly every type of caged-disc prosthesis, and it is not always accompanied by abnormal valve sounds. Auscultation is not always helpful in diagnosis because slight alterations in sounds and minimal regurgitation may not be detected, even when they exist. Undoubtedly, the durability of caged disc valves is enhanced when the disc rotates freely within the cage about an axis perpendicular to the disc surface so that wear is evenly distributed. If the disc motion is restricted by thrombus formation or other impediment,[8] uneven wear, notching of the periphery and eventual jamming may occur.

A previous phonocardiographic study[12] of 28 patients with Kay-Shiley caged disc mitral valves established a range of systolic time intervals expected for that valve series. Intervals measured were Q wave to closing click (range 31 to 100 msec, mean 67 msec, standard deviation [S.D.] ±16.8), A_2 to opening click (range 57–182 msec, mean 104 msec, S.D. ±32.4), and the duration of the opening click (range 18 to 58 msec, mean 34 msec, S.D. ±9.9). The Index of Wells, difference of Q wave to closing click minus A_2 to opening click expressed in hundredths of a second, was derived (range +1.7 to −10.3 units, mean −3.7

TABLE I

Acoustic Changes in Prosthetic Mitral Caged Disc Valves

Reference	Prosthesis	Prosthetic Valve Sounds	Murmurs	Comments
Carey and Hughes[8] (1968)	Kay-Shiley (obsolete model)	Normal	Absent	Autopsy showed disc edge severely grooved and motion restricted by misplaced suture
Mullen et al.[9] (1970)	Kay-Shiley (obsolete model)	Normal	Systolic	Patient reoperated upon to remove fibrin between sewing ring and disc
Stross et al.[10] (1971)	Starr-Edwards model 6500	Normal (2 cases)	Faint systolic (1 case)	Autopsies showed fibrinous material on struts prevented closure
Horsley et al.[2] (1969)	Starr-Edwards model 6500	Decreased intensity	Absent	Abnormal disc motion caused by fibrous tissue on struts
Demaney and Zimmerman[3] (1970)	Kay-Suzuki	Opening click almost absent	(Not stated); mitral regurgitation by cineangiography	Patient reoperated upon to remove massive clot obstructing orifice and causing disc to cock
Leachman and Cokkinos[4] (1969)	Cooley-Cutter (5 cases); Kay-Shiley (1 case)	Faint or absent opening click (6 cases)	Absent (4 cases); systolic (2 cases)	2 deaths, 4 reoperations; 5 cases of valve detachment
Edgett et al.[11] (1967)	Cross-Jones (2 cases); Hufnagel (2 cases)	(Not stated)	Loud systolic (in only case detailed)	Intermittent failure to close; disc cocking attributed to uncorrected aortic regurgitation in 3 cases
Low and Lefemine[5] (1967)	Kay-Suzuki	Absent	Loud systolic	Autopsy showed disc jammed in cocked position
Vasko and Leighton[6] (1968)	Hufnagel	Absent	Systolic	Reoperation for disc jammed in cocked position
Samaan[7] (1969)	Hammersmith	Absent	(Not stated)	Autopsy showed disc jammed in cocked position
This study (1973)	Kay-Shiley (obsolete model)	Double opening click	Absent	Double opening click disappeared after embolic episode; thrombus fragment recovered from patient's leg; patient later died (no autopsy)

units, S.D. ±3.3). For comparison, the data of von Klein[13] for eight patients with Kay-Shiley valves were Q wave to closing click 65 msec mean, A_2 to opening click 125 msec mean, and Index of Wells −4 to −8 units. The mean Q wave to closing click and A_2 to opening click intervals reported here for mitral caged disc valves are only slightly less than the corresponding intervals reported for mitral caged ball valves.[14]

The Q wave to closing click and the A_2 to opening click intervals were within the expected range in the patient's phonocardiographic tracings before and after embolization (Fig. 1). The additional sound occurring approximately 90 msec after the onset of the first opening click had not been observed previously. The extra opening click persisted for 10 months but disappeared after the patient's first embolic episode. The significance of this sound was not recognized until it was noted that the recovered embolic fragment mated closely with the cage strut of a new prosthetic valve of the same model and size as the patient's prosthesis (Fig. 2).

Mechanism and significance of double opening click: The Kay-Shiley series K prostheses have sili-

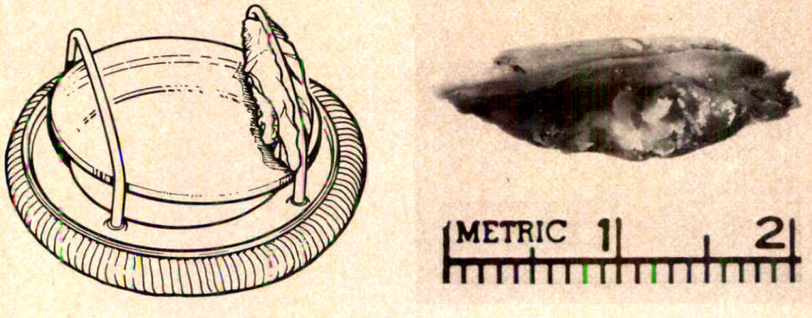

FIGURE 2. Thrombus fragment recovered from the patient's left femoral artery. At **right,** photograph of the elongated thrombus fragment; note the groove along the entire length. At **left,** artist's conception of the excellent match noted when the fragment was mated to the cage strut of a new valve prosthesis of the same model and size as that previously implanted.

cone rubber discs. Other investigators[14,15] have observed double or multiple opening clicks caused by mitral caged ball valves with silicone rubber poppets. Usually, the extra opening sounds associated with the bounce or flutter of a ball poppet are of diminished intensity compared to the initial opening sound caused by impact of the ball and cage. In our case, the two opening clicks were of about the same intensity. It does not seem likely that a second disc-cage impact subsequent to disc rebound caused by elastic recoil was responsible for the second opening click, especially since the double sound was not present in the patient initially. Nor is it likely that the second click, which appeared and then disappeared after the embolic episode, was a third heart sound. Hultgren and Hubis[14] recorded a prosthetic third sound of diminished amplitude in nearly 80 percent of a series of patients with mitral caged ball valves. They suggest that the prosthetic third sound of ball valves is due to (1) relative motion between ball and cage caused by movements of the prosthetic valve and mitral annulus during atrial systole and early diastolic ventricular filling or, possibly, (2) transient reversal of the atrioventricular pressure gradient at the time of rapid ventricular filling. Double or multiple opening clicks normally do not occur in caged disc mitral valves. Because our patient had no evidence of aortic valve disease it is unlikely that the double sound noted was caused by a cocking phenomenon associated with uncorrected aortic regurgitation as suggested by Edgett et al.[11]

Autopsy was not performed, and thus the presence or extent of thrombus formation on the cage struts was not known. If thrombus was present and then partially dislodged, as the evidence suggests, the double opening click must have been associated with the impediment to disc motion (Fig. 2, left). Disc motion would have been greatly altered if: (1) Motion of the confined edge of the disc under the thrombus probably was very limited or nonexistent. (2) Uniform up-and-down motion of the disc was prevented, and its motion was similar to that of a cocked disc or pivoted leaflet, thus leading to (3) altered hemodynamics, the generation of transient and possibly highly asymmetric eddies, and the development of nonuniform forces on the surfaces of the disc.

It is reasonable to assume that the first opening click was caused by the free edge of the disc at the moment of its impact with the cage strut. The second opening click could have resulted from (1) another impact of the free edge on the cage strut, or (2) impact of the confined edge of the disc on the orifice of the valve during a retrograde motion of that edge. In the first mechanism, considered the most likely explanation, either of the two factors suggested by Hultgren and Hubis[14] and mentioned previously could have been responsible. It is also possible that a wobbling, erratic disc motion and altered hemodynamics could have led to the second mechanism. However, continued thrombus growth during the 10 month existence of the double opening click could have totally incarcerated the less mobile edge of the disc, and thus the second sound would have disappeared even without fragmentation and embolization of thrombus.

The results presented here illustrate that phonocardiography can often provide important information on dysfunction of mitral caged disc prostheses. More often than not, changes in prosthetic valve sounds are an ominous sign of impending, and perhaps catastrophic, malfunction. However, the absence of such altered sounds does not always preclude existing dysfunction.

Acknowledgment

We thank the Moore-White Medical Foundation, Los Angeles, California, for donating the phonocardiographic equipment used in this study.

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Multiple Coronary Arteriosystemic Fistulas

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A 58 year old man presented with angina pectoris and no heart murmur. On selective coronary angiography, multiple coronary arteriosystemic fistulas involving all three major coronary arteries were found. This is the first such case reported. It is speculated that this vascular anomaly represents persistence of embryonic intertrabecular vessels that permit the coronary arteries to communicate with the left ventricular chamber through the Thebesian vessels.

Congenital coronary fistula is not a rare anomaly.[1] The majority of these fistulas form an arteriovenous connection between a coronary artery and the right heart chambers. In most reported cases, the abnormal fistula involves only one coronary artery. This report describes a unique case in which multiple arteriosystemic fistulas connected each of the coronary arteries with the left ventricle.

Case Report

A 58 year old man was admitted to the hospital for evaluation of recurrent chest pain of more than 10 years' duration. Retrosternal pain occurred with physical exertion and was relieved by rest and administration of nitroglycerin. For the previous 2 years, the pain had increased in frequency and duration, occurring at rest and after meals. The patient entered another hospital 3 weeks before this admission because of chest pain lasting 20 minutes. After acute myocardial infarction was ruled out, he was transferred for cardiac catheterization and selective coronary angiography. There was no history of dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, ankle swelling, high blood pressure or heart murmur. Past medical history and family history were negative.

Physical examination revealed a blood pressure of 130/70 mm Hg and a regular pulse of 70/min. The neck veins were flat and the lungs clear. Examination of the heart revealed no abnormal heaves or thrills. The point of maximal impulse was felt in the fifth left intercostal space and midclavicular line. A fourth heart sound was heard along the lower left sternal border. No murmurs were audible.

Multiple blood tests, which included complete blood count, lipid profile and cholesterol, urea, uric acid and serial enzyme determinations, were within normal limits. A glucose tolerance test indicated the presence of diabetes mellitus. Roentgenographic studies revealed no evidence of chamber enlargement. The electrocardiogram disclosed normal sinus rhythm and small R waves in leads V_1 to V_3 and nonspecific abnormal S–T and T waves in the left precordial leads.

Cardiac catheterization revealed a normal cardiac output and increased left ventricular end-diastolic pressure (19 mm Hg). Use of a platinum tip electrode and hydrogen inhalation studies ruled out intracardiac left to right shunts. A left ventricular angiogram demonstrated a normal end-diastolic chamber and contractile pattern. Selective coronary angiography revealed that all the coronary arteries were dilated, elongated and tortuous (Fig. 1). Calcification involved the main left coronary artery and the proximal left anterior descending and left circumflex arteries. Studies of the right coronary artery demonstrated a markedly dilated posterior descending branch. The contrast material streamed into and opacified the left ventricular chamber

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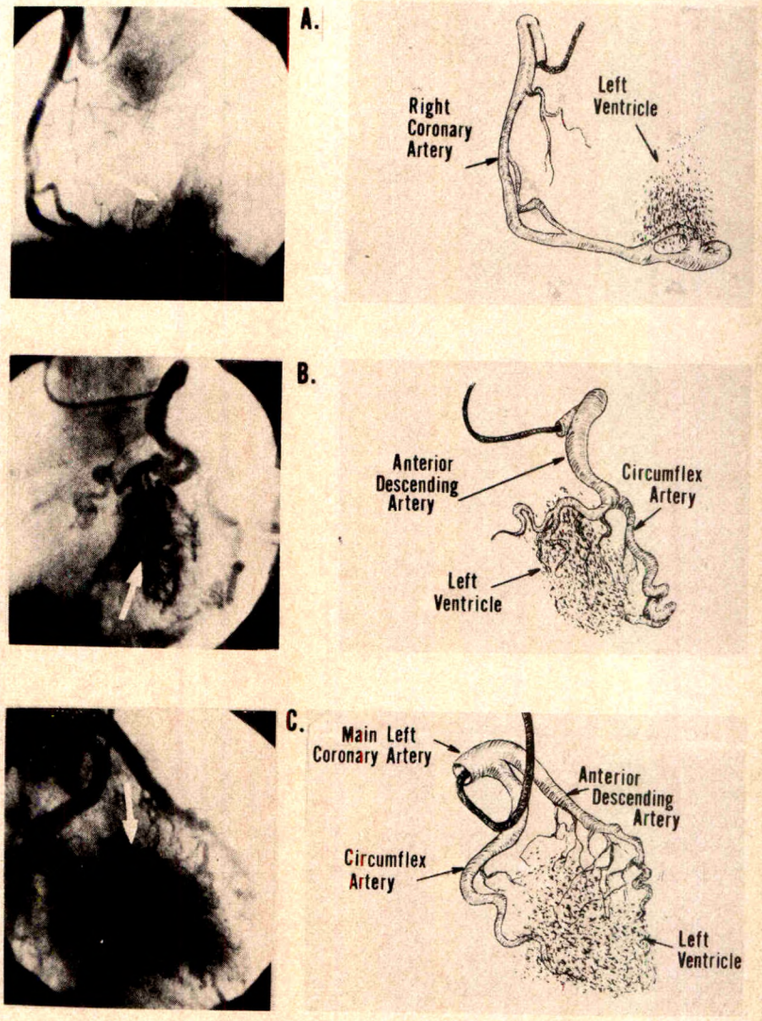

FIGURE 1. Selective coronary angiographic study. Actual cine frames are shown at left and a sketch of the same frame is shown at right. **A,** selective right coronary angiogram in the left anterior oblique projection. **B** and **C,** selective left coronary angiograms in the left anterior oblique **(B)** and right anterior oblique **(C)** projections. These frames were taken during diastole. During systole, the contrast material in the left ventricular chamber was washed out in the aorta. Note that all the major arteries are dilated and elongated.

through a maze of fine vessels (Fig. 1A). Similarly, opacification of the left anterior descending and circumflex arteries delineated a maze or plexus of small, fine vessels surrounding these arteries, with contrast material streaming into the left ventricular chamber and completely opacifying the cavity (Fig. 1, B and C). This opacification of the left ventricle occurred only during diastole with injection of contrast material into the right or left coronary artery; during systole, the contrast material was washed out into the aorta.

Discussion

Coronary arterial fistulas usually arise from a single artery, most frequently the right coronary artery, and usually communicate with the right ventricle, right atrium or pulmonary artery.[1] A review[1] of 172 reported cases revealed only 4 in which the fistula involved both the right and left coronary arteries. In the case described here, all three major coronary arteries had fistulous connections with the left ventricle. A coronary arterial fistula emptying into the left side of the heart is uncommon; when it occurs, the fistulous connection tends to involve the left atrium rather than the left ventricle.[1]

In nine reported cases[1–6] of a coronary fistula emptying into the left ventricle, the right coronary artery was involved in three,[1–3] the left anterior descending artery in one[4] and the left circumflex artery in one.[1] The involved coronary artery was not specified[5] in one patient, and in three cases described by Abbott et al.,[6] only the presence of an aberrant vessel was indicated, with no mention of involvement of the major coronary arteries. Thus, the present case is unique in that all three major coronary arteries formed an arteriosystemic fistula.

Selective coronary angiograms demonstrated marked dilation of the right, left anterior descending and circumflex arteries. The diameter of these arteries at their origin (6, 7 and 6 mm, respectively) was almost twice that reported as normal by Baroldi and Scomazzoni.[7] Coronary fistulas may be formed by a well defined vessel emptying into a cardiac chamber or, as in our case, by a plexus of multiple fine vessels. This vascular maze probably represents persistence of embryonic sinusoids that are usually obliterated in normal development. The myocardial vessels in the

adult heart are derived embryologically from both endothelial protrusions into the myocardium and coronary arteries and veins.[8] This endothelial protrusion into the myocardium extends to the epicardial surface, forming an intertrabecular network. The outermost intertrabecular network becomes almost completely obliterated and forms a capillary network as the myocardium grows, whereas the innermost intertrabecular vessels retain their communication with the chambers of the heart, forming the Thebesians vessels of the adult heart. Investigators[4,5,9] reporting earlier cases, in which sinusoidal communication existed between involved coronary arteries and the heart chamber, ascribed the anomaly to persistence of the outermost intertrabecular space, thereby permitting a communication between the coronary artery and heart chamber through the Thebesian vessels. A similar mechanism can explain the angiographic findings and diffuse involvement in our case. The reason for abnormal communication only with the left ventricle is not clear.

In our case, no murmur was heard suggesting a coronary artery fistula. Such fistulas have been associated with continuous[1,3] or purely diastolic murmurs.[2] In the case reported by Lovitt and Lutz,[4] no heart murmur was mentioned and the fistula was discovered only on postmortem examination. The cause of death in that patient was not related to the fistula. The symptoms of angina pectoris in our case can be attributed to the coronary fistulas. The anticipated hemodynamic burden of arteriosystemic fistulas would be diastolic overload of the left ventricle. The normal pulse pressure and the absence of left ventricular hypertrophy in our case suggest that there was no hemodynamically significant volume overload on the left ventricle. The patient's symptoms should be treated medically.

Acknowledgment

We thank Dr. Irwin Hoffman for reviewing this manuscript and express gratitude for the assistance given by Mrs. Miriam Posner, Mr. Joshua Hamby and Mrs. Brenda Hamby.

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Ventricular Dysfunction in Coronary Artery Disease

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The past decade has seen increasing acceptance of both coronary arteriography and left ventriculography as integral to the evaluation of patients with suspected coronary artery disease. The former is essential for accurately mapping coronary pathologic anatomy whereas the latter serves two distinct purposes: (1) delineation of zones of abnormal ventricular wall motion, and (2) characterization of the overall performance of the ventricle by determination of changes in ventricular volume and shape throughout the cardiac cycle. Measurement of ventricular end-diastolic and end-systolic volumes allows the stroke volume to be normalized in relation to the volume at the onset of systole, that is, the ejection fraction. Thus, left ventriculography aids in the evaluation of the heart as a fluid-displacement pump. This of course is not a new concept, but one that has been overshadowed in the past by the more traditional hemodynamic view of the ventricle that is usually expressed in terms of end-diastolic tension-length and volume-work relations (Starling effect). In addition to these concepts, this discussion will also consider the applicability of measurements that characterize the heart as a force or pressure generating muscle, rather than as a volume pump.

Dynamic Morphology of the Left Ventricle

We can obtain important data about the size, shape and ejection pattern of the heart chambers from the ventriculogram. Studies of the motion of individual segments of myocardium can provide information about local disturbances in contraction (asynergy) as well as information about the residual contractile pattern of normal zones of the ventricle.

Ventricular wall motion abnormalities: Approximately 35 percent of patients referred to our department for the assessment of clinical coronary artery disease show a normal ventricular contraction pattern at rest.[1] The remaining 65 percent will demonstrate some type of resting left ventricular asynergy. Prior studies[1-5] have reported that these abnormalities are most commonly seen in patients with previous myocardial infarction, but asynergy can also occur without evidence of infarction. The patterns may range from the classic well demarcated bulging left ventricular aneurysm to various types and degrees of abnormal motion of a segment of the heart without change in overall contour. Asynergic segments may be dyskinetic, akinetic or hypokinetic (asyneretic),[1] and the area may be composed of muscle or scar, or both. A disturbed temporal sequence of contraction (asynchrony) may also be observed.

Stress-induced asynergy: One might hypothesize that a pattern of ventricular contraction which is normal at rest could be disrupted during acute ischemia, at which time segmental or global wall motion may abruptly become abnormal. This has been observed experimentally in animals.[6] In man, wall motion may be studied during a stress known to precipitate ischemia, such as tachycardia induced by rapid atrial pacing.[7,8] The demonstration of a new asynergic zone on a ventriculogram under such conditions suggests deficient perfusion of that myocardial segment. This can provide critical information about the severity or significance of a given local coronary arterial obstruction. Such stress-induced asynergy may be the mechanical equivalent of other signs of ischemia, such as alterations in the repolarization phase of the electrocardiogram, or the production of lactate by the myocardium as evidence of glycolysis.

Wall motion augmentation during inotropic stimulation: Conversely, when the resting ventriculogram is abnormal, the effect of an intervention that augments contraction might provide valuable information. Although the abnormal zone in some patients may appear isolated and surrounded by normally contracting muscle, in others poor contraction of ventricular wall may be quite extensive without clear-cut demarcation between normal tissue, viable but nonfunctioning ischemic muscle and frank avascular scar. Furthermore, overall contractile activity may be depressed below its usual level for a variety of reasons. The differentiation of those segments of muscle potentially capable of being stimulated has great clinical importance. Two inotropic interventions are under investigation: *l*-epinephrine, and the potentiated postextrasystolic beat. *L*-epi-

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ıephrine was selected because it increases stroke 'olume and ejection rate without inducing major 'hanges in blood pressure or heart rate. Further- nore, it has little primary effect on the coronary vas- ulature so that coronary blood flow increases pari)assu with oxygen demand. In normal subjects given ın infusion of 1 to 3 μg/min, *l*-epinephrine uniformly ıugmented the segmental contraction pattern in all :ones of the ventricle.[9] This was associated with an ncrease in stroke volume and ejection fraction. In he subjects with coronary artery disease, all zones hat were normal in the control ventriculogram ex- ıibited an augmented contraction pattern, whereas :ones of asynergy showed either improved contrac- ion, no change or, rarely, a worsening of contrac- ion. Thus, in certain patients with coronary artery lisease, *l*-epinephrine unmasked zones of previously ıoncontracting muscle that appeared capable of shortening with inotropic stimulation. In others, this agent demonstrated zones that were apparently in- capable of any contractile response and presumably were irreversibly damaged. Similar results have re- cently been obtained by analysis of the augmented (potentiated) contraction that occurs after a ventric- ular premature beat.[10] Using a pulse generator with an impulse appropriately timed for the QRS cycle, a ventricular premature beat can be safely introduced during the course of the initial resting ventriculo- gram. The augmented beat can be compared with a control beat during the same ventriculogram.

Both of the techniques described define potential contractile reserve not only in normal segments, but also in marginal or even apparently scarred zones. These data may be of help in determining which areas to revascularize, although it is not known if muscle that responds to an inotropic stimulus will have a similar response solely if local blood supply is improved. These techniques may also be useful in in- dicating which patients will require augmentation of contractile state after cardiopulmonary bypass, and even in indicating clearly which ventricular wall seg- ments are totally refractory to inotropic stimulation and may conceivably be excised.

Ventricular volume measurements: Ventricular wall motion can be analyzed quantitatively as well as qualitatively. For quantitative analysis the ventri- cle is assumed to be ellipsoidal and both long (base to apex) and transverse diameters are drawn from angiographic silhouettes. (A catheter in the coronary sinus can be used to provide a fixed reference point.[5]) Wall motion can thus be described in terms of axial or hemiaxial shortening of the base, body and apex of the ventricle. If the film is calibrated to life size (by a grid system, for example) volumes can be measured throughout the cardiac cycle using the area-length method of Dodge et al.[11] These investi- gators noted close agreement between ventricular volume determined by biplane angiograms of post- mortem casts, and the known volume of the casts. However, in the beating heart with abnormal wall motion, the ventricle is often asymmetrical, particu- larly in its minor axes, and the relation of angio- graphic to true volumes may be less certain. In addi- tion, considerable scatter can occur between volumes calculated from biplane and single plane data in pa- tients with ventricular asynergy.[2] (Addition of the left anterior oblique view is useful in such patients since it allows analysis of two zones, septal and post- erolateral, not visualized in the conventional right anterior oblique view.) It had been hoped that echo- cardiography could be used to determine ventricular volumes in patients with coronary disease, as has been done in other cardiac diseases, but the presence of asynergy makes echo-angiographic correlations ten- uous and the value of echocardiograms in measuring volume often questionable.[12]

Relation of Morphology to Hemodynamics

Ventricular diastolic (filling) pressure: In many patients with ventricular asynergy, left ventricular end-diastolic pressure is often elevated and cardiac output reduced. This is more common in patients with global than in those with regional abnormalities of wall motion, and least common in patients with a normal contractile pattern.[1] Even in patients with normal hemodynamic status at rest, exercise or pac- ing-induced tachycardia may precipitate elevations in left ventricular end-diastolic pressure (and asyner- gy) with or without clinical angina.[13] Whether these abnormalities reflect alterations in ventricular com- pliance (due presumably to ischemia or fibrosis, or both) or are a sign of true left heart failure is un- clear. Certainly, when filling pressure is increased throughout diastole, cardiac output is more likely to be reduced and clinical failure more obvious. Such an increase in mean diastolic pressure is often associ- ated with a filling gallop (the third heart sound), ob- viously a helpful clue for the clinician.[14] When filling pressure is increased only at end-diastole, clinical congestive failure is less common. It may be that the fourth heart sound heard in many of these patients heralds the presence of a stiff rather than a failing ventricle.

Ejection fraction: The basis for abnormal ventric- ular function curves in patients with coronary artery disease also remains unclear. Even though the re- sponses to atrial pacing, exercise, pharmacologic in- terventions and angiographic contrast medium serve as useful stress tests,[15] the clinical and prognostic importance of a depressed ventricular function curve obtained under these circumstances has not been re- solved. Because of technical problems in defining pressure-volume relations in the intact ventricle (for example, distinguishing alterations in ventricular compliance from transient episodes of left heart fail- ure), it may be more useful to characterize the ven- tricle mainly in terms of fluid displacement. Fluid displacement has traditionally been thought of in terms of cardiac output, but cardiac output is a product of both heart rate and stroke volume and is influenced by the peripheral circulation as well as the autonomic nervous system. An index that ap- pears potentially more useful is the systolic ejection fraction obtained from ventriculography. (Since ven-

triculography provides a *continuous* record of ejection it has advantages over other techniques that measure only end-diastolic and end-systolic volumes.) As a function of both stroke volume and end-diastolic volume, the ejection fraction is normalized for each ventricle. Thus, a reduced ejection fraction can be due to a reduced stroke volume with a normal end-diastolic volume, or to a normal stroke volume delivered from an increased end-diastolic volume, as in dilatation. Because it is the slope of the ventricular function curve, the ejection fraction can be considered a rough index of myocardial contractility (at normal afterloads). It may be of help in defining expected risks for immediate and intermediate term survival after coronary artery bypass procedures, as well as in assessing the degree of myocardial decompensation in the face of borderline or questionable values for left ventricular end-diastolic pressure and cardiac output. This index also has value in patients with valvular heart disease since changes in the ventricular size, shape and contraction patterns of such patients may aid in the preoperative evaluation of myocardial reserve. When considering ejection fractions in either coronary or valvular heart disease, however, it is important to remember that these values can vary ±0.05 percent from one study to the next in the same patient, even when hemodynamic states are comparable.[16] Differences in interpretation of silhouettes by observers may also lead to similar disparities. Displacement can also be measured as a function of time: the normalized mean velocity of circumferential (transverse axis) fiber shortening, or VCF.[17] Although readily obtainable from continuous ejection-phase ventriculographic silhouettes, the value of either the ejection fraction or VCF in cases of gross asynergy is uncertain. In such instances, extensive aneurysmal segments may obscure the contribution of normally contracting zones, thereby yielding falsely low values for both of these variables. In these patients direct measurement of *segmental* hemiaxial shortening is a preferable method for evaluating regional myocardial performance.

Contractility indexes: Another approach in assessing ventricular dysfunction is to consider the ventricle as a force or pressure generating muscle, rather than as a pump. Contractility indexes derived from isovolumic (preejection) phase pressure recordings are based on the assumption that there is symmetrical contractile effort and uniform fiber length throughout the duration of isovolumic systole. While theoretically applicable in ventricles free of segmental disease, and with normal impulse conduction, such an assumption may not be tenable in patients with coronary artery disease, although promising results with one such index have recently been reported.[18] As noted previously, patients with coronary artery disease often lack topographic and temporal uniformity of ventricular contraction. In addition, the extent to which mechanical asynergy alters series elasticity is not known, and normal values for myocardial contractility may actually be due to a falsely low coefficient of series elasticity. Thus, it is critical to know the ventricular contraction patterns in any patient whose cardiac function is to be judged by isovolumic indexes.

TABLE I

Hemodynamic Abnormalities Correlated with the Extent of Vessel Disease in 100 Patients with Coronary Artery Disease

	Vessels Involved*		
	1 (29 Cases)	2 (33 Cases)	3 (38 Cases)
LVEDP (mean ± SEM) (% of patients with > 12 mm Hg)	16.0 ± 2.5 (41%)	15.5 ± 2.4 (53%)	17.1 ± 3.0 (53%)
Ejection fraction (mean ± SEM) (% of patients with < 0.50)	0.60 ± 0.04 (25%)	0.58 ± 0.07 (23%)	0.51 ± 0.05 (37%)
Cardiac index (mean ± SEM) (% of patients with <2.51/min per m²)	2.8 ± 0.1 (25%)	2.8 ± 0.1 (25%)	2.5 ± 0.2 (35%)
Asynergy (% of patients)	49%	68%	72%

* >75 percent stenosis.
LVEDP = left ventricular end-diastolic pressure.

Interrelations Among Morphology, Hemodynamics and Arterial Lesions

Regional ischemia is the hallmark of coronary heart disease, with metabolic and electrocardiographic abnormalities related to the areas of myocardium subserved by the obstructed vessel.[19] This is also true of abnormalities of ventricular wall motion. In general, the frequency of asynergy increases with the severity of the vascular disease, and collateral vessels do not protect against either the development of asynergy or of hemodynamic abnormalities.[20] On the other hand, akinetic regions may be associated with single vessel disease, and normal contractile patterns can persist despite multivessel disease. Similarly, hemodynamic abnormalities are not always correlated with the extent of vessel disease.[20] This is true not only in terms of mean values for left ventricular end-diastolic pressure, cardiac index and ejection fraction, but more importantly in relation to individual subjects with hemodynamic abnormalities. Thus, in a recent series of 100 consecutive patients studied in our department, mean values for these variables were not significantly different in patients with one, two or three vessel disease (Table I). Although there *was* a greater frequency of these hemodynamic abnormalities in patients with more extensive disease, these differences also did not achieve statistical significance. In the patients with a normal left ventricular end-diastolic pressure at rest, the response to angiographic contrast medium was also similar in all three subgroups. It would appear that even after stress the development of abnormal dynamic morphology and hemodynamics may bear no direct relation to the extent of vessel involvement. This is different from the positive correlation often

observed between multivessel disease and the frequency and severity of postexercise ischemic electrocardiographic changes.[21] Therefore, the clinician cannot be sure of the extent of coronary artery disease in patients with obvious ventricular dysfunction (cardiomegaly, diastolic heart sounds, for example) and, conversely, multivessel disease suggested by findings on the resting[22] or postexercise electrocardiogram[21] does not preclude normal ventricular function.

Future Directions

The preceding discussion has emphasized the importance of left ventriculography in evaluating ventricular dysfunction, in relation both to wall motion abnormalities and to the ability of the heart to displace fluid adequately. What are needed in the future are: (1) Better clarification of the underlying pathophysiology of this dysfunction. Is it due to altered compliance, transient failure, incomplete relaxation, or a combination of these abnormalities? (2) More stringent determination of the *clinical* usefulness of the various indexes of ventricular performance, including those obtained by noninvasive techniques. This is especially important for evaluating the results of medical and surgical therapy. (3) Finally, new techniques that define as accurately as possible irreversibly scarred or nonfunctioning areas of ventricular wall.

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Second Degree Atrioventricular Block

A Matter of Definition

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Clinical Heart Block. Dropped beats: When the grade of block is higher the ventricle fails to respond to occasional auricular impulses. This form is rarely simple.

Sir Thomas Lewis
The Mechanism and Graphic Registration of the Heart Beat (1925)

The use of His bundle and other intracavitary recordings[1] in recent years has led to a greater understanding of abnormal atrioventricular (A–V) conduction and has made possible exceptionally accurate diagnoses.[2] However, most clinical decisions on treatment and prognosis are made on the basis of conventional surface electrocardiograms. The question then arises whether the traditional classification of second degree A–V block into two types is clinically adequate considering the recently reported exceptions[3] to the old dictum that the lesion resides in the A–V node in type I second degree A–V block and in the His-Purkinje system in Mobitz type II block. This leads to a further question: Exactly what constitutes each type?

At the beginning of this century, John Hay[4] and Wenckebach[5]—working without an electrocardiograph—independently recognized two types of second degree A–V block. From an analysis of venous and arterial pulses, Hay inferred that one type was a disturbance of conduction and the other a disturbance of excitability. In 1924, Mobitz,[6] introducing the terms type I and type II, described his type II as "the first step to Adams-Stokes attacks and complete permanent dissociation." Thus, the prognostic significance of this distinction has been known for nearly 50 years.

Treatment and prognosis of a patient with second degree A–V block depends on many factors including the patient's history and the degree of block and its lowest site. Because a decision may have to be based on the manner in which beats are dropped, it is essential to define very strictly the type with a poor prognosis.

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Definitions

Katz and Pick[7] wrote in their classic text, "In Type II, which is rare, dropping out of ventricular beats takes place without warning, that is, it occurs after a series of beats with a constant, either normal or prolonged P–R duration." Outlining the salient diagnostic features of A–V block, they noted that in second degree A–V block (as opposed to advanced A–V block), ". . . each QRS can be related to a preceding P wave but intermittently a *single* P wave is not followed by a QRST." Of type II they wrote, ". . . there is a constant duration of P–R (normal or prolonged) in all beats *except for the first one (or two) after the pause—which may show variation.*" More recently, many authors have come to refer to Mobitz type II A–V block as an arrhythmia characterized by failure of a *single* impulse to conduct to the ventricles in the absence of antecedent prolongation of the P–R interval (normal or prolonged). This definition unfortunately lends itself to more than one interpretation. Moreover, block in the His-Purkinje system does not necessarily qualify as a type II block.[8] Several points need to be clarified.

1. *Constancy of the P–R intervals before and after the dropped beat*[4,6,9–14]: Hay[4] and Mobitz[6] appreciated this point and indicated it in ladder diagrams in which the ventricular intervals containing the blocked beat are twice the basic cycle length (Fig. 1D). Consequently, shortening of the P–R interval after a blocked impulse represents either a type I sequence or an escape beat in an otherwise typical Mobitz type II pattern[14] (Fig. 1E).

2. *Lack of progressive lengthening of the P–R intervals before the dropped beat:* Long type I sequences are often atypical (Fig. 1B) and may exhibit several constant P–R intervals before the dropped beat[14–16] (Fig. 1C). In this situation, type I block simulates type II block, and, indeed, the pattern has been called type II block by several authors.[17–21]

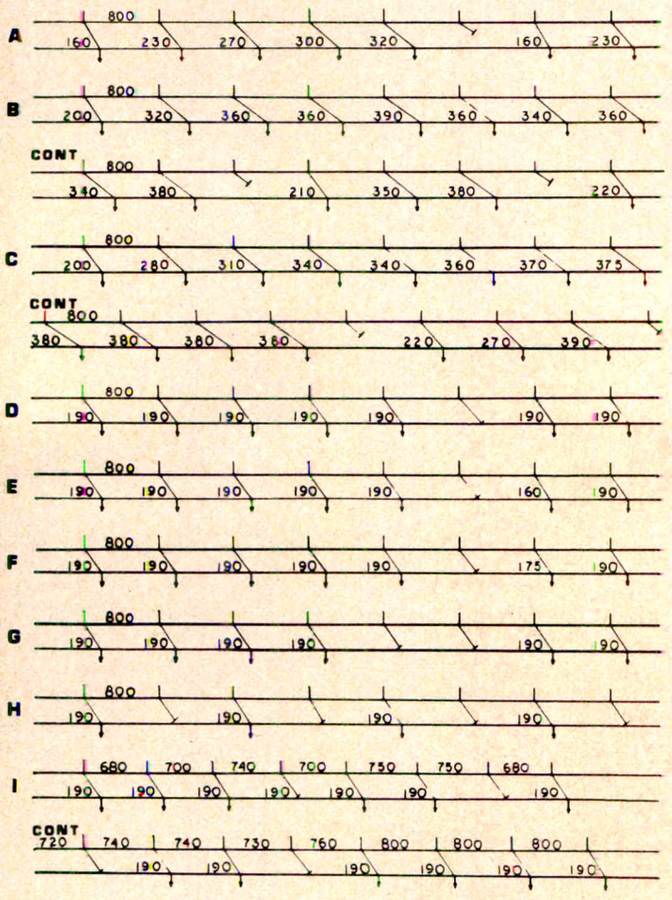

FIGURE 1. Second degree A–V block. The three levels represent activation of the atria, A–V junction (P–R intervals are shown between the lines) and ventricles, respectively. All values are in milliseconds. **A,** classic type I A–V block. **B,** relatively long and atypical type I sequence. Note the irregular fluctuations of the P–R intervals before the dropped beat. **C,** relatively long and atypical type I sequence with several constant P–R intervals before a dropped beat. Note the shorter P–R interval after the blocked P wave. This pattern has been confused with type II block. It is essential to examine *all* the P–R intervals in long rhythm strips and not merely several P–R intervals (as in the lower part of **C**) preceding a blocked impulse. **D,** true type II A–V block. Every impulse traverses the A–V node successfully, and therefore the structure is not afforded a long recovery time as in the classic Wenckebach phenomenon.[12] **E,** dropped beat without warning followed by a 30 msec shortening of the P–R interval. This may represent either type II block with an escape beat or a type I block with an unmeasurable increment in the second P–R interval. **F,** type II A–V block according to the criteria of Langendorf et al.[32] **G,** high degree A–V block: Failure of conduction of two consecutive P waves without warning. The unchanged P–R interval of the first conducted beat after the blocked impulse suggests infranodal block. **H,** fixed 2:1 A–V block. This cannot be classified, but persistence of the fixed conducting ratio associated with a normal P–R interval suggests infranodal block. **I,** sinus arrhythmia with type II block. Note the constancy of the P–R intervals despite the changing sinus cycles.[9]

Close inspection of *long* rhythm strips permits differential diagnosis. Narula[14] recently emphasized the following points: (1) Marked prolongation of the P–R interval suggests A–V nodal disease. (2) Examination of all the P–R intervals reveals distinct shortening of the P–R interval in the first conducted beat (and perhaps subsequent beats) after the blocked beat (Fig. 1C). The purist might argue that an escape beat can never be excluded in this situation, but the same unrealistic argument would also apply to the opening beat of every typical type I sequence. (3) Long type I sequences often change their conducting ratios spontaneously (for example, from 15:14 to 4:3) and then show classical type I behavior (Fig. 1C). (4) Interventions such as administration of carotid sinus pressure, atropine, amyl nitrite or performance of exercise or atrial pacing may be helpful if conducting ratios do not change spontaneously.[22,23] Clinically these measures are rarely required if sufficiently long rhythm strips are taken.

3. *2:1 and higher degrees of block:* To be certain that the P–R intervals are not progressively prolonged, it is essential to have at least two consecutive conducted P waves. It follows that a fixed 2:1 or higher degree of A–V block should not be classified as either type I or type II, regardless of the site of block or the duration of the QRS interval[24] (Fig. 1H). Yet, isolated 2:1 A–V block has recently been labeled type II.[25,26] Mobitz[6] pointed out that 2:1 or higher degrees of A–V block could originate from either a type I or type II sequence. In an individual case, the significance of such block can usually be evaluated by noting the company it keeps, particularly during the relatively frequent change in conducting ratios.

4. *Block, without warning, of two or more consecutive atrial impulses:* This type of block has been called Mobitz type II A–V block by some investigators,[13,14,27–30] and Langendorf and Pick[31] suggested calling it a "more advanced form" of Mobitz type II block. It is probably best designated simply as block of high degree. In this situation, regardless of nomenclature, a constant P–R interval before and after the blocked beats suggests an infranodal lesion (Fig. 1G). In addition, to avoid further confusion, classification of block as type I or II should be restricted to second degree block and should not be extended to complete A–V block.

5. *Sinus arrhythmia:* The influence of changes in sinus rate upon type II A–V block is rarely commented upon. Relatively small fluctuations of rate during spontaneous sinus arrhythmia do not affect the typical Mobitz type II pattern of constancy of all P–R intervals before and after the dropped beat[9] (Fig. 1I).

Langendorf et al.[32] recently stated that " . . . it is strange that the differentiation of the two types of second degree A–V block has not received more at-

tention. This is partly due to the imperfect definition of Type I." The imperfect definition of type II has also detracted from its prognostic significance as originally conceived by Mobitz. Consequently, the differentiation of type I and type II second degree A–V block should be focused on a more rigid definition of type II block. Accordingly, an arrhythmia that does not fit the rigid definition of type II block may well be type I block and thus requires further evaluation.

We may now arrive at a strict clinical definition of type II A–V block, as follows: Type II A–V block may be diagnosed from the conventional electrocardiographic tracing if the P–R intervals of all beats (provided there are at least two consecutive conducted P waves to be examined) *before* and *after* a single blocked beat are not measurably different.

The Wenckebach phenomenon is not completely synonymous with type I A–V block. Although a progressive increase in the P–R interval in successive beats is usually followed by a dropped beat, the sequence may terminate with an echo beat, reciprocating tachycardia or other arrhythmia. The P–R intervals may be variable and apparently haphazard when there is marked sinus arrhythmia, fluctuating vagal tone or a long series of conducted beats before the dropped beat. We can now quite simply define type I A–V block as follows: It is the intermittent failure of A–V conduction of a single beat (known not to be of type II) associated with inconstant A–V conduction times. There will, of course, be cases in which the distinction cannot be made confidently; these cases should not be classified until more evidence is available. Usually such evidence can be provided by sufficiently long electrocardiographic tracings or by fairly simple interventions such as administration of carotid sinus pressure, amyl nitrite, or other agents. In rare cases, complicated procedures such as atrial pacing and intracavitary recordings may be necessary.

Clinical Significance

Type I block generally occurs in the A–V node and type II in the common bundle or its branches. There are rare exceptions. The occurrence of the Wenckebach phenomenon in the His-Purkinje system has now been established beyond question in experimental animals,[33,34] man (surface electrocardiogram[35–38] and His bundle recordings[8,12,14,39–46]) and microelectrode studies of isolated fibers.[47–49]

His bundle studies have demonstrated a strong correlation of type II A–V block (according to the proposed definition) with His-Purkinje (infranodal) lesions.[12,14,39,40,50–59] The type II pattern has not yet been established as arising from the A–V node in experimental animals[18–21] or man[17] despite recent claims,[17–21] for in the cases cited atypical type I sequences are likely because the P–R (or A–H) interval shortens after the dropped beat. Langendorf et al.[32] recently reported an example of type II block occurring above the site of recording of the His potential, but His electrograms cannot distinguish a lesion in the lowest part of the A–V node from one in the proximal His bundle. The diagnosis of type II A–V block from the conventional electrocardiogram therefore has considerable clinical usefulness because the data closely reflect the anatomic site of disease.

Recent studies have further blurred the distinction between type I and type II block. In over 200 microelectrode experiments on conduction in the peripheral His-Purkinje system, Anderson et al.[48] found true type II block in only 2 studies. However, they recorded numerous examples of *apparent* type II block in which a type I pattern with very small increments of conduction (less than 10 msec) could be demonstrated when the data were displayed at very rapid speeds. El-Sherif et al.[34] came to similar conclusions on experimentally induced second degree A–V block. They pointed out that a recording speed of 200 mm/sec could not detect increments of a few milliseconds in the H–V interval; however, at this speed they were able to demonstrate increments of 5 to 15 msec invisible on the conventional electrocardiogram.

Decremental conduction thus appears to be the common denominator of depressed conduction. In the A–V node the increments of conduction are usually large and recognizable on a conventional electrocardiogram. In the His-Purkinje system, the increments are often very small and may be detectable only with special recording techniques. Consequently, the observation of type I A–V block with consistently small increments in conduction time should suggest the possibility of infranodal block. In this situation His bundle recordings are particularly helpful. Clinically, however, block in the His-Purkinje system usually appears as an all-or-none phenomenon on the conventional electrocardiogram[14,60] and rarely exhibits visible type I sequences. Some authorities have allowed slight shortening of the first (and second[8]) P–R interval, [7,24,61,62]—duration of no more than 20 msec according to Langendorf et al.[32]—in diagnosing type II block. If the phrase "type II block" is replaced by "infranodal block," the statement becomes more appropriate and less ambiguous.

Concealed His bundle extrasystoles may mimic type II block. Rosen et al.[63] used His bundle recordings to document the existence of pseudo A–V blocks secondary to premature nonpropagated (concealed) His bundle depolarization.[64] Damato et al.[65] subsequently demonstrated in elegant dog experiments that concealed His bundle extrasystoles could produce an electrocardiographic pattern indistinguishable from typical Mobitz type II block. More recently, Narula,[14] who studied six such cases with His bundle recordings, emphasized that concealed His bundle extrasystoles have essentially the same significance as Mobitz type II block because they are almost invariably associated with severe disease of the His bundle. His contention is supported by similar findings in the six cases of Grolleau et al.[66]

Clinical implication: When considered in perspective, these rare but interesting exceptions lend further credence to the value of the ordinary electrocardiogram as a reasonably accurate way of evaluating A–V block at the bedside. The overwhelming ma-

jority of type I blocks occur in the A–V node, and true Mobitz type II blocks represent infranodal lesions. In this context, His bundle recordings play a relatively small part. Despite the challenges of new methods of investigation, the old concept of two types of A–V block has emerged unscathed although the need for stricter definitions and provocative discussion is clear and pressing.

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Current Status of Circulatory Assist Devices

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Although it has been over a decade since Clauss and collaborators[1] described a counterpulsation pump for patients with cardiogenic shock, there is still no uniform agreement that this form of therapy has a role in the management of these critically ill patients. Theoretical considerations lead to a conclusion that counterpulsation should be able to affect favorably the balance between myocardial oxygen supply and demand. Ventricular afterload and wall tension are decreased by the sudden reduction in aortic systolic pressure during pump diastole, thus leading to a reduction in oxygen demand by the myocardium.[2] Coronary blood flow and oxygen delivery to the myocardium increase as the level of central aortic diastolic blood pressure is raised during pump systole.

Since the introduction of a counterpulsation pump, many devices have been developed to support the failing myocardium. These have ranged from pump oxygenators such as those utilized during open heart surgery to totally noninvasive external pressure suits that compress the limbs. Several questions may be asked: (1) What have we learned about the syndrome of cardiogenic shock in recent years? (2) What is the role of cardiac assist devices in the management of cardiogenic shock? (3) Do cardiac assist devices have applications other than in patients with cardiogenic shock?

Syndrome of Cardiogenic Shock

Use of the Swan-Ganz catheter has allowed a more precise characterization of patients with true cardiogenic shock as opposed to those with myocardial infarction and hypovolemia. In both conditions systemic arterial pressure and cardiac output are decreased and calculated peripheral vascular resistance is almost always increased. In hypovolemic shock, however, central venous pressure is nearly always reduced and pulmonary arterial wedge pressure is usually less than 10 mm Hg. In cardiogenic shock the central venous pressure is either normal or increased, and the pulmonary arterial wedge pressure usually exceeds 18 mm Hg.

Although patients with cardiogenic shock have a poor prognosis, the precise mortality rate varies from series to series. It is likely that at least part of the reason for this variability is the grouping of patients with hypovolemia and hypotension together with those who have true cardiogenic shock. Knowledge of filling pressures on the left side of the heart has helped to identify and separate these two subsets of patients. Replacement of the osmotic or colloid volume, thereby raising left-sided filling pressures, is often sufficient to increase arterial pressure and cardiac output in the patient with hypovolemia. Volume replacement in the patient with true cardiogenic shock is to no avail. For a diagnosis of true cardiogenic shock, the systolic arterial pressure should be less than 80 mm Hg or at least 80 mm Hg less than the patient's normal blood pressure; the cardiac index should be less than 2.1 liters/min per m^2 and urinary output less than 20 ml/hour; perfusion to the brain and periphery should be diminished so as to cause mental obtundation, cold clammy skin, ashen color and pre-terminal appearance. The mortality rate in true cardiogenic shock so defined is almost 100 percent. To the degree that patients with hypovolemia are included in reports of patients with cardiogenic shock, the mortality statistics diverge from 100 percent.

The pathologic changes in the heart of patients who die with cardiogenic shock were described by Page et al.[3] Their study demonstrated that cardiogenic shock is related to the extent of myocardial damage and that, during prolonged severe shock, continuing focal myocardial necrosis occurs. Nineteen of 20 patients with acute myocardial infarction and cardiogenic shock had lost 40 to 70 percent of left ventricular myocardium. In contrast, 12 of 14 patients with myocardial infarction but without evidence of shock had lost 30 percent or less of left ventricular muscle.

The study further demonstrated a border zone between clearly infarcted muscle and normal muscle. This zone was characterized by cells in various stages of damage and necrosis, thus indicating that cellular injury is likely to be progressive during the period of shock. These findings can be reproduced in the experimental production of acute infarction in animals, as shown by Cox et al.[4] After ligation of a coronary artery, three distinct zones can be identified by histochemical staining techniques. A central area shows disruption of the normal myocardial architecture and complete absence of all demonstrable

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enzymatic activity. This area is surrounded by a second, intermediate zone that shows evidence of mitochondrial swelling but, in general, preservation of normal myocardial architecture. A third zone is normal. Cox et al. demonstrated that the intensity of the changes and the size of the zones increase over time and that the combined area of necrosis and injury reaches maximal size 18 hours after infarction. Between 18 hours and 1 week after infarction, the total size of affected muscle remains stable but the necrotic zone enlarges at the expense of ischemic tissue. One week after infarction only a narrow ring separates necrotic tissue from normal myocardium. It is possibly in the boundary zone that techniques to salvage myocardium may have their most important implications for the prevention and therapy of cardiogenic shock.

Role of Cardiac Assist Devices in Therapy of Cardiogenic Shock

The introduction of intraaortic balloon pumping added a new dimension to the therapy of patients with cardiogenic shock secondary to acute myocardial infarction.[5] Over the past decade this technique has been utilized by several investigators, and their results can now be placed in clinical perspective.[6-8] The early hope that this form of cardiac assistance would markedly alter the prognosis of the patient with cardiogenic shock has not been realized. Although some patients are undoubtedly alive because of this device, the mortality rate associated with this syndrome still exceeds 75 percent. Recognition that intraaortic balloon pumping alone was not sufficient to assure salvage of a larger number of patients led to efforts to offer appropriate candidates aortocoronary saphenous vein bypass grafts with the hope of salvaging sufficient myocardium to help the patient survive the acute myocardial infarction.[9] Again, although a small number of patients have been saved by this procedure, the overall mortality rate is still 75 percent. This approach should be considered in appropriate patients, however, since it is likely that the mortality rate would be close to 100 percent without it.

Other Applications of Cardiac Assist Devices

Pathologic study of myocardial tissue after an acute myocardial infarction suggests that there is a demonstrable gradation of damage.[4] An identifiable zone of ischemic injury surrounds the necrotic area of myocardium. Over the course of approximately a day the area of necrosis enlarges as ischemic muscle undergoes irreversible changes due to anoxia. The area of ischemic tissue has been referred to as the boundary zone. There is recent experimental evidence that myocardium from the ischemic zone may be salvaged after a myocardial infarction.[10] Interventions that cause an increase in myocardial oxygen consumption, such as administration of isoproterenol and digitalis, led to an enlarged zone of ischemic change on the epicardial electrocardiogram. Conversely, increase of arterial pressure, even though it augmented myocardial oxygen consumption, decreased the extent of ischemic injury. It was concluded from these observations that in the presence of coronary occlusion the changes in coronary perfusion pressure exert a greater and more deleterious influence on the extent of myocardial ischemia than do the changes in myocardial oxygen consumption resulting from increased arterial pressure.

Successful counterpulsation usually results in a reduction of aortic systolic pressure, ventricular afterload and myocardial oxygen requirements. Counterpulsation also leads to an augmentation of aortic diastolic pressure and coronary perfusion pressure. These effects were demonstrated in a series of experimental animals subjected to coronary arterial occlusion and studied by epicardial electrocardiogram.[11] The use of propranolol to decrease myocardial oxygen requirements during intraaortic balloon pumping was also studied.[12] This combination greatly reduced myocardial oxygen consumption. Whether pharmacologic interventions, counterpulsation or combined techniques will ultimately prove salutary to the patient with myocardial infarction and cardiogenic shock is still not certain but the idea of salvaging ischemic myocardium deserves considerably more investigation. The possibility that counterpulsation may one day be utilized to salvage ischemic myocardium not only in patients with myocardial infarction and cardiogenic shock, but also in patients with uncomplicated myocardial infarction is intriguing. Toward this end there has been increasing interest in the development of a noninvasive technique of counterpulsation that might have application to a larger number of patients.

In 1963 several investigators reported on a method of external counterpulsation that did not involve cannulation of blood vessels.[13-15] The external method of counterpulsation can be applied rapidly and requires no operative manipulation. There is no extracorporeal handling of blood, thus obviating the need for anticoagulant agents. This method applies pulsed pressures to the lower limbs during diastole, thereby returning blood to the central circulation and augmenting aortic pressure. Synchronous with the R wave of the electrocardiogram, the cuffs are deflated so that the left ventricle does not eject against increased peripheral resistance. In 1968 work began on an external counterpulsation device that applies pressure initially at the ankle and then in a sequenced manner to the thigh.[16] The rationale for sequenced pulsation in contrast to nonsequenced external pulsation is based on theoretical considerations on the effect of externally applied pressure to various-sized vessels in the limb. Large vessels with a small ratio of wall thickness to lumen size collapse more readily in response to externally applied pressure than do smaller vessels with a large ratio of wall thickness to lumen size. A uniformly applied external pressure to a limb would be anticipated to collapse the larger, proximal vessels first, thereby impeding return of blood to the central aorta. In man it is not known whether one method of external coun-

terpulsation will have an advantage over the other. Sequenced external counterpulsation was compared with intraaortic balloon pumping in a series of animal studies before and after induction of cardiogenic shock.[17] Although the degree of diastolic augmentation was equivalent with both modes of cardiac assistance, the increase in cardiac output was greater in the studies using external counterpulsation. This finding may reflect the augmentation in venous as well as arterial blood during external assistance.

A report[18] of alleviation of angina pectoris after treatment with external counterpulsation warrants special notice since the number of potential candidates for this form of therapy is legion. Twelve patients with severe angina pectoris were pain-free after 4 days of treatment with counterpulsation for 1 hour a day. In addition, improvement in the angiographic appearance of the coronary arteries was noted in approximately half of the patients studied 4 to 8 weeks after counterpulsation.

If this aspect of external cardiac assist proves to be of value as a mode of therapy for patients with angina pectoris, an enormous number of patients may benefit. This event would also signal an unanticipated evolution in the development of cardiac assist devices. Originally intended solely for the most critically ill patient with cardiogenic shock, early use of cardiac assistance to salvage ischemic myocardium has become a distinct possibility. Its use in the patient with angina pectoris extends its application far beyond that originally conceived. It may be that the largest group of patients who might benefit from cardiac assistance were not considered as candidates until recently.

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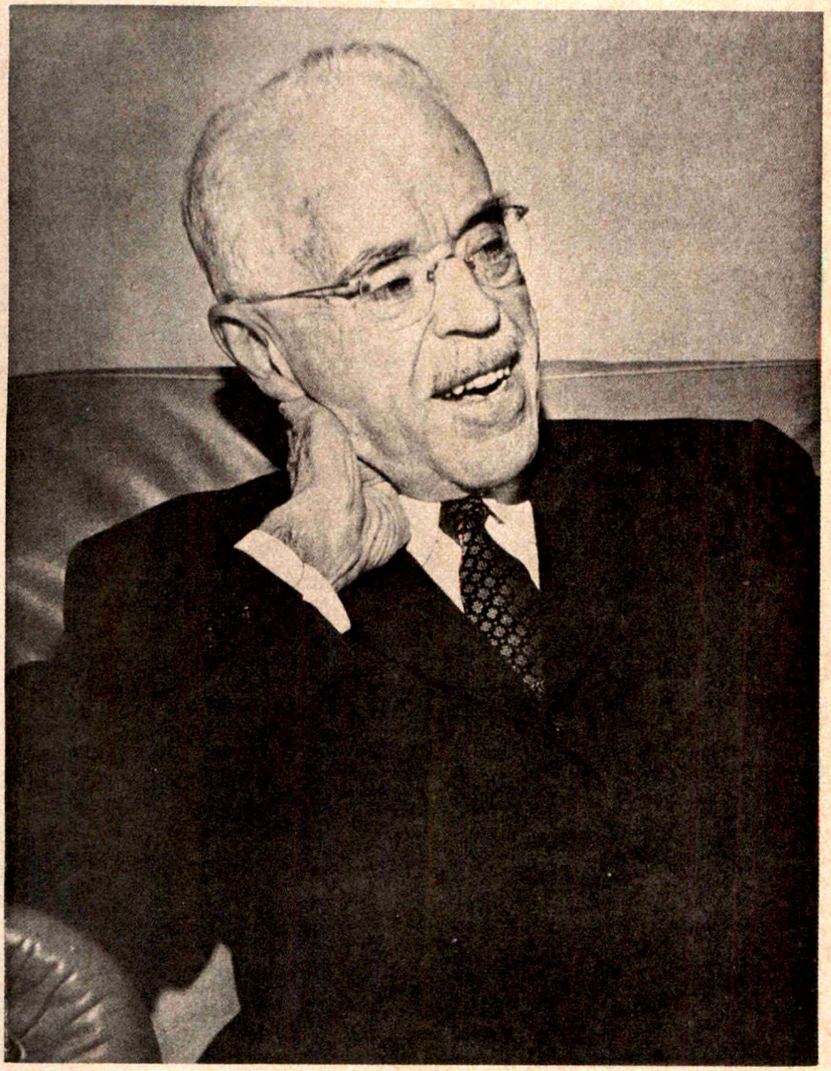
Paul Dudley White 1886–1973



J. M. Gauthier

Paul Dudley White

The Full Life

Paul Dudley White is dead and in the fullness of my thoughts I cannot say a single remark of sadness or grief. Dr. White's life was an exuberant one and he lived a wonderful span of 87 years and 5 months. His ability to perform, to think, to stimulate, to savor, to be agile and active continued to the very end. He began as the neophyte in American cardiology and became its father and grandfather. His sense of joy, his gaiety, his energy, his curiosity carried him and his message of *optimism* throughout the world.

Paul White's passing marks the end of the era in which American cardiologists had their origin in England and Europe. The remarkable galaxy who returned from their experience with Thomas Lewis included Paul White, Sam Levine, Frank Wilson, Louis Katz, Roy Scott, Robert Stroud, William Kerr, Arthur Master and other memorable workers. That era ends and another generation picks up the torch.

All of us now on the scene are, in a real sense, students of Paul Dudley White. Between his house staff years beginning in 1914 at Massachusetts General Hospital and his death there on October 31, 1973, he was the Dean of the world of cardiology. The man goes, the legend remains.

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ECHOCARDIOGRAM IN *d*-TRANSPOSITION OF GREAT VESSELS

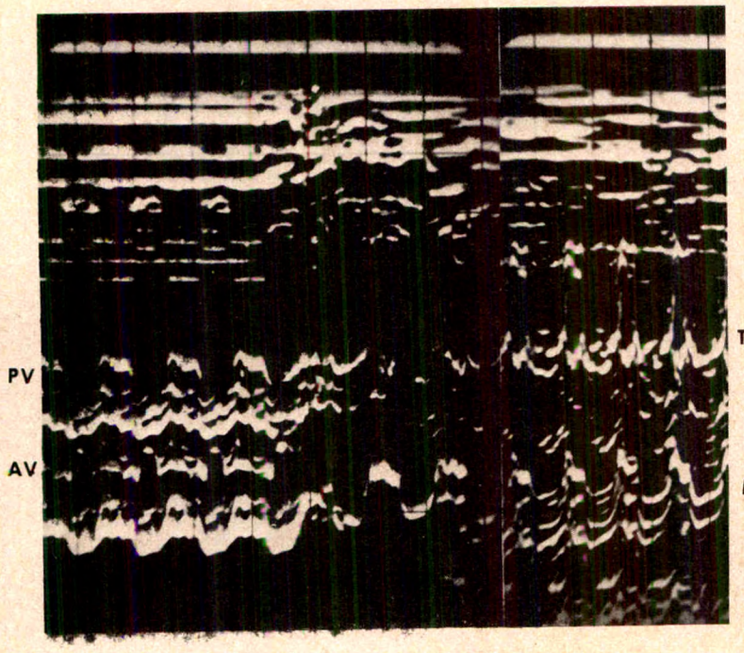

FIGURE 1. Case 1, a normal 30 hour old premature infant. The echocardiogram demonstrates simultaneous recording of the aortic valve (AV)—the posterior semilunar valve in this normal infant—and the pulmonic valve (PV). MV = mitral valve; TV = tricuspid valve.

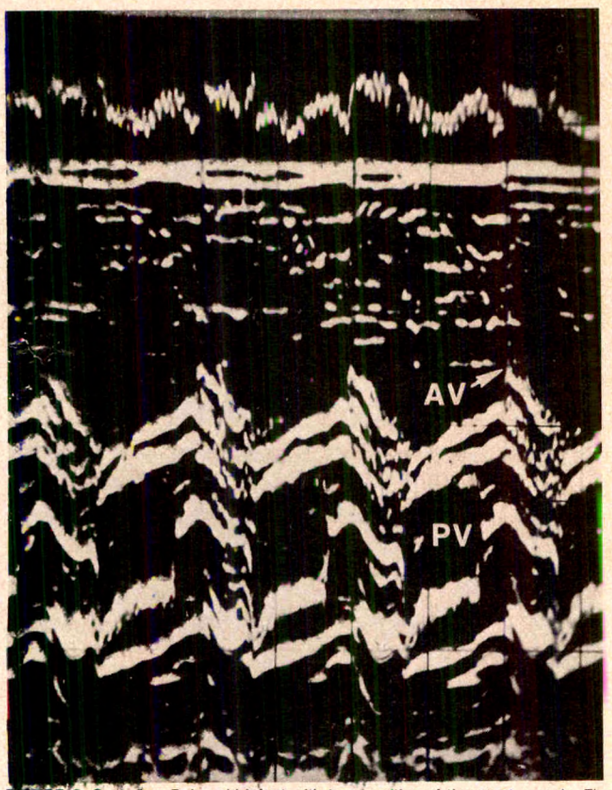

FIGURE 2. Case 2, a 7 day old infant with transposition of the great vessels. The echocardiogram demonstrates simultaneous recording of both semilunar valves: the posterior, pulmonic valve (PV) and the anterior aortic valve (AV).

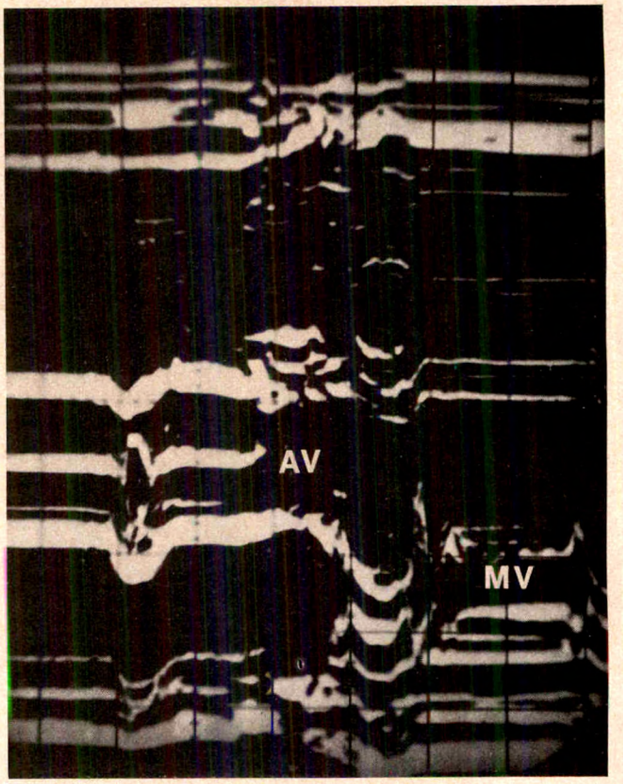

FIGURE 3. Case 1. The echocardiogram demonstrates normal aortic-mitral valve (MV) continuity.

Dillon et al.[1] in their recent article on *d*-transposition of the great vessels state that "the echocardiographic finding of superimposition of the great vessels without intervening crista together with simultaneous recording of the semilunar valves is diagnostic for transposition of the great vessels." They stress the importance of simultaneous semilunar valve echoes in the diagnosis of transposition.

In a group of 6 patients with *d*-transposition of the great arteries proved by cardiac catheterization, we had similar findings. The patients' ages were 16 hours, 4 days, 6 days, 7 days, 20 months and 8 years, respectively. In all six, we demonstrated superimposition of the great arteries as well as simultaneous recordings of the semilunar valves.

Although these findings are almost invariably seen in transposition we have also observed them in a 30 hour old twin premature baby with an autopsy-proved normal heart obtained shortly before he died of streptococcal sepsis. In an echocardiographic examination (Fig. 1) we were able to demonstrate simultaneous semilunar valve echoes similar to those occurring in transposition (Fig. 2). Since the infant had a normal heart, the posterior semilunar valve is the aortic valve, and the anterior valve is the pulmonic valve; in transposition (Fig. 2), the posterior valve is the pulmonic valve, and the anterior is the aortic valve. We were also able to demonstrate normal aortic-mitral continuity in this infant (Fig. 3).

This is the first and only case in which we were able to record simultaneously the two semilunar valves in a normal infant. The phenomenon could have been due to rotation and malformation of the heart after repeated external cardiac massage.

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1. **Dillon JC, Feigenbaum H, Konecke LL, et al:** Echocardiographic manifestations of *d*-transposition of the great vessels. Am J Cardiol 32:74–78, 1973

DR. DILLON REPLIES

I agree with Glaser et al. that positional or rotatory changes within the chest may lead to abnormal echocardiographic findings and we alluded to this in our recent paper. In review of their three illustrations, I have the following comments: In Figure 1 I am not convinced that the top echo labeled PV is in fact the pulmonic valve. I think this is the chordo-reminense of the tricuspid valve. We see this often in adults, and certainly the view to the right preceding the white line indicates that this top structure is not the pulmonic valve but probably part of the posterior leaflet of the tricuspid valve or part of the supporting chordae of that valve. In addition, I see no anterior wall structure that I would interpret as an artery. Above what is labeled pulmonic valve there is a 2 1/2 to 3 1/2 cm area in which there is no anterior "vessel" wall. I think this would be present in a truly double-barreled situation. In Figure 2 I am less convinced than the authors on the basis of one Polaroid snapshot that this is a case of transposition. I agree with the authors' interpretation of Figure 3.

I am in no way trying to be critical of the work of Drs. Glaser, Whitman and Liebman, and I want them to be encouraged to try to prove or disprove our recent thesis. But I honestly believe that Figure 1 cannot be given the interpretation they have provided.

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BOOK REVIEWS

MYOCARDIAL INFARCTION, by Eliot Corday, MD and H. J. C. Swan, MD. Baltimore, Williams & Wilkins, 1973, 398 pages, $26.50

A plethora of changing concepts, new techniques and old theories concerning myocardial infarction have stimulated two authorities to expand the knowledge on this major clinical problem. Their book logically proceeds with the pathophysiologic findings, diagnosis, arrhythmias, prognosis and early care of the patient with coronary disease. Chapters on cardiogenic shock, therapeutics and surgery are comprehensive and cautiously optimistic. The primary authors have harnessed the talents of many experts in their respective specialties.

The practicing physician with an intellectual curiosity in basic physiology will find the section on pathophysiology beautifully written and a necessary prelude to understanding the remaining text. The chapters on diagnosis commence with an analysis of noninvasive techniques and summarize present knowledge on altered enzymes. Flotation catheters receive more critical discussion by a pioneer in their development, Dr. Swan. In another excellent chapter, radioisotopic dynamic imaging is well illustrated as a reliable noninvasive technique capable of detecting many of the complications of myocardial infarction such as mitral insufficiency, aneurysm or pericardial effusion.

Brief chapters on contractile performance, echocardiography in determining left ventricular dimension and mass as well as the clinical application of left ventricular pressures are pertinent, practical and devoid of minutiae. The section on diagnosis is terminated by several chapters on cardiac arrhythmias. Reciprocal rhythm as a form of reentry is succinctly covered and well illustrated. A weaker chapter on aberrant conduction versus ventricular tachycardia includes no graphic material. To the electrocardiographer, this chapter is superfluous and to the student, abstruse. A more comprehensive chapter on cardioversion is followed by a brief one on cardiac pacing. This latter section is somewhat superficial; little mention is made of fascicular blocks and their management.

A major section on cardiogenic shock attacks this problem from multiple aspects. Unfortunately, there is some duplication in the discussion of positive inotropic agents as well as circulatory assistance using ascending aortic synchronized pulsation, but the overall analysis is complete and current.

The final section on therapeutics heralds the latest views on the growing armamentarium of medical and surgical treatments and includes a discussion of the psychological management of the patient with coronary disease. Perhaps it may be a surprise to some and gratifying to all that use of oxygen and morphine is experimentally efficacious and clinically sound. Nitroglycerin and phentolamine are given separate chapters, whereas digitalis ignominiously occupies a brief paragraph in a section on intractable heart failure. At least a chapter on digitalis toxicity in myocardial infarction might have been appropriate. The discussion of surgical management in myocardial infarction covers the gamut of acute infarctectomy, aneurysmectomy and revascularization. The final chapter attempts to identify the patient whose cardiogenic shock is a manifestation of profound ischemia, resulting from severe proximal arterial occlusion, the focal point for emergency revascularization.

This book represents a well written, well illustrated and timely analysis of the literature on myocardial infarction blended with personal observations by keen, clinical cardiologists. It is primarily directed to the internist and clinical cardiologist. Its comprehensiveness should mark it as a standard reference in the field today.

Mark G. Cohen, MD
Wilmington, Delaware

RECENT ADVANCES IN CARDIOLOGY, edited by John Hamer. Baltimore, Williams & Wilkins, 1973, 424 pages, $21.75

Though it resembles a yearbook or annual review, this volume is both more ambitious in depth and broader in its scope than the usual book of this genre. The 16 chapters, written by 12 contributors each of whom is, or has been, associated with the "British school" of cardiology, make up a well written survey of selected topics ranging from "Pediatric Cardiology" and "Surgery of Ischaemic Heart Disease" to chapters on "Myocardial Metabolism."

Most chapters represent a useful survey of recent, or historical, developments. Each is provided with a long bibliography; however, the references lack titles, which somewhat diminishes their usefulness. The writing is lucid, the text unmarred by the unpleasant staccato rhythm characterizing the yearbook chapter that is sometimes merely a pastiche made from the summaries of other articles. It is gratifying to this reviewer to find that at least 4 of the 16 chapters deal with the application of basic biochemical, biophysical and pharmacologic principles to clinical cardiology. One hopes that this emphasis will, if continued, permit the British to maintain their great heritage, exemplified by Sir James MacKenzie, Sir Thomas Lewis, Paul Wood and others, of utilizing newly emerging scientific knowledge to improve the care of the patient with cardiac disease.

Because this book is not intended to be a comprehensive review of cardiologic topics, it cannot be compared to heavier and more detailed textbooks. Neither is it a monograph of limited scope, and thus it cannot replace the many volumes devoted to one or another of the specialized areas in cardiology. With few exceptions, notably a thorough and most informative chapter on the "Pharmacology of Beta-Adrenoceptive Antagonists," each chapter represents a survey, so that the reader who wishes to obtain a detailed picture of the topic must utilize the bibliography. Yet as a "practical guide for postgraduate students and physicians" this book is successful and so can be recommended to the internist who wishes to review the background of modern cardiologic practice.

Arnold M. Katz, MD, FACC
New York, New York

AN INTRODUCTION TO RESPIRATORY PHYSIOLOGY, by Frederick F. Kao. Excerpta Medica, Amsterdam, American Elsevier, New York, 1972, 325 pages, $20.00

The omnipotence of Bates et al. and Comroe et al. in the area of pulmonary physiology may cause a new author to hesitate before entering the field. Dr. Kao need not have

paused; he has written a gem. Although his book is an outgrowth of a lecture course in respiratory physiology given to medical students over the course of a decade, it is by no means of value only to the medical student; it can compete with the well established texts for the attention of physicians and physiologists with a specific interest in the lungs.

The twelve chapters range from a simple introduction and a chapter on principles, in which Dr. Kao displays a mastery of physics, to the truly sublime—"Respiration in Deep Sea, at High Altitudes, and in Outer Space." Each chapter builds logically upon its predecessor. Introductory paragraphs and clear diagrams present an overall concept to be elucidated in the ensuing pages. "Working questions" follow, which help the reader gauge his grasp of the preceding material (answers are provided at the end of the book). Finally, each chapter contains an exhaustive list of reference and reading material. The chapter on "Regulation of Ventilation" contains ten pages of references, and Dr. Kao's brilliant review of this complicated subject is reason enough to own this book.

Although Dr. Kao almost fanatically avoids the clinical (imagine a book about pulmonary physiology without one mention of bronchitis or emphysema!), his book will serve as a constant source of reference to clinicians. Each new issue of our journals adds to the rapidly changing knowledge about pulmonary function in disease. We must turn to texts for our knowledge of fundamentals, and in this volume these foundations have been superbly presented.

Alvin S. Teirstein, MD
New York, New York

ECHOCARDIOGRAPHY, by Harvey Feigenbaum, MD, assisted by Sonia Chang, BS. Philadelphia, Lea & Febiger, 1972, 239 pages, $11.00

The recent surge of interest in clinical echocardiography has been hampered by the absence of any single source of information in this field. This volume amply fills that void.

After a short historical overview, a simplified description of the underlying physical principles of echocardiography and the equipment available is presented. There is a well illustrated chapter on the techniques and pitfalls in obtaining good echocardiograms. Technique pertinent to examining individual structures is reemphasized in subsequent chapters dealing with specific structures. Heavy emphasis is rightly placed on the mitral valve and on pericardial effusion which are areas of prime clinical diagnostic interest. Separate chapters are also devoted to the "state of the art" in evaluating the aortic, tricuspid and pulmonic valves, right ventricle, left atrium and atrial tumors, with a brief introduction to congenital heart disease included. Two important chapters deal with the echocardiographic contribution to the study of left ventricular function and coronary artery disease, both areas of intensive investigation.

Central to the success of this book are the illustrations and photographs, both of excellent quality. However, more detailed labeling of some photographs would be helpful for beginners. A very useful feature is the large number of photographs in general and of difficult-to-examine structures in particular, such as the posterior mitral leaflet and atrial myxoma. The listing of references within the text and the appendix containing normal values are useful additions.

This book is highly recommended for all interested in echocardiography whether they wish to learn the technique themselves or just the basic diagnostic features and potential for clinical diagnosis.

Monte Bodenheimer, MD
New York, New York

VECTORCARDIOGRAPHY, by Alberto Benchimol, MD. Baltimore, Williams & Wilkins, 1973, 223 pages, $18.50

This volume is intended to define the role of vectorcardiography in clinical cardiology and clearly sets forth the criteria for the diagnosis of specific abnormalities. Although it is primarily based on observations with the Frank system, various other lead systems are compared and many of the data can be extrapolated to them. The usual chapters devoted to fundamentals of atrial and ventricular activation, chamber hypertrophy, bundle branch block and myocardial injury are profusely and clearly illustrated. Of particular interest is the well organized chapter devoted to hemiblocks, which appears to be quite up to date and complete. The value of timed vectorcardiography or "running loops" in identification of arrhythmias and in interpretation of interventricular conduction disturbances is nicely shown. The use of simultaneously recorded His bundle electrograms provides clear documentation of the author's presentation. The bibliography following each chapter appears to have been thoughtfully selected. In its entirety, this book clearly reflects the extensive experience of the author and his familiarity with the techniques described. Although too sophisticated for a primer or introductory text, it is highly recommended to all those with an interest in electrocardiography or vectorcardiography, or both, as a worthwhile learning experience and reference book.

Melvin Kahn, MD
New York, New York

CARDIO-RESPIRATORY RESUSCITATION, by Alan Gilston and Leon Resnekov. Philadelphia, F. A. Davis, 1971, 310 pages, $16.00

Refinements and advances in the care of the cardiac and respiratory patient over the past 10 years have created a vast literature on the subject. Therefore, it is a welcome relief to find a text that neatly combines the pertinent elements of cardiac and pulmonary resuscitation with the basic points required in each area to manage properly the problems that arise. The approach is clinical and physiologic, with major emphasis on the practical elements of both as applied to patients requiring resuscitation.

Gratifying, also, is the attention focused on the use of mechanical ventilators, a subject not often emphasized, even in some of the better training programs. The section on arterial blood gas analysis and the presentation of the pros and cons of endotracheal intubation and tracheostomy are informative and succinctly correlated with the important applications of mechanical ventilation and effective weaning of patients from respirators. However, I am not in agreement with the authors' statement (page 199) that "measurements of ventilation and blood gas analysis are not important in a conscious patient during weaning" and that "what really matters is the patient's clinical state." The clinical assessment of effective venti-

lation should continue to depend on arterial blood gas monitoring as well as evaluation of the clinical state of the patient.

The text is of specific value to medical students, physicians in training, practicing physicians and paramedical personnel employed in intensive and coronary care units. For those physicians well versed in the elements of cardiopulmonary resuscitation, the book provides a useful general review.

Leonard D. Epifano
Yonkers, New York

CARDIAC SURGERY, edited by John C. Norman, MD. New York, Appleton-Century-Crofts, 1972, 703 pages, $20.00

The second edition of this volume presents significant detail on all aspects of cardiac surgery in 34 chapters by 54 contributors. The organization of chapters will help the student find pertinent topical information.

Many of the chapters are outstanding. The physiologic basis of cardiac surgery is presented in admirably balanced detail. The chapter on anesthesia for cardiac surgery clearly reflects the author's large experience and mastery of the field. The discussion of the mechanics of cardiopulmonary bypass provides a sound background for the beginner. Material on surgical techniques for cardiopulmonary bypass and perfusion techniques is pertinent and vivid. Other good chapters from the general section deal with metabolic responses to extracorporeal circulation, preservation of myocardial metabolism, hyperbaric oxygenation and the treatment of cardiac arrest. The remainder of the book is divided into five sections on cardiac surgery in infants and children, and in adults, complications, recent developments and future prospects. With one notable exception, the chapters in all of these sections succinctly present the background position of the cardiac surgical art today. The chapter on surgery for coronary artery disease is written in a dogmatic tone that is inappropriate to this rapidly developing field. Categorical statements about techniques of coronary arteriography, the prognosis of arteriographic lesions, indications for operation and preferable surgical techniques will probably be misleading to the inexperienced. The quality of the illustrative angiograms is poor. With the exception of this chapter, the new edition of Norman's Cardiac Surgery is a useful guide to the field.

George E. Green
New York, New York

BIOMEDICAL ELECTRONICS, second edition, by Howard N. Yanof, PhD. Philadelphia, F. A. Davis, 1972, 545 pages, $22.00

The first half of this volume, entitled "Fundamentals of Electronics," is a valuable and well written treatise couched in terms easily understood by a physician with some familiarity with the subject. The second half, entitled "Biomedical Instruments," covers a few important subjects on a more practical level. There are chapters on transducers and bioelectric measurements. One, on "The Output Signal and What To Do with It," is essentially a discussion of recorders.

The treatment of transducers is exhaustive and excellent, and particularly valuable to the cardiologist, although echocardiography is given short shrift. The chapter on measurements enters into inappropriate details of neuroanatomy. In the review of recorders, there is a surprising absence of reference to the Electronics for Medicine oscillograph, an instrument that has contributed much to the development of cardiac catheterization, from Cournand and Richards to the present day.

Dr. Yanof's book is particularly recommended for the cardiologist interested in acquiring a basic understanding of modern electronics. The subject of biomedical electronics is, of course, too extensive to be covered by a single volume of 565 pages and thus this book does not succeed as a reference text.

Alvin I. Gordon
New York, New York

REVIEWS IN CARDIOLOGY*

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* Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue (Amer J Cardiol 28: 366–967, 1971).

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

FEB. 11–14 **Twenty-third Annual Scientific Session.** H. J. C. Swan, FACC, president. Americana Hotel and New York Hilton, New York, N. Y.

FEB. 15–17 **1974 Reconvened Annual Scientific Session.** Carlos E. Bertran, FACC, director. Hyatt Hotel, San Juan, P. R.

MAR. 18–22 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Mt. Sinai Medical Center, New York, N. Y.

MAR. 21–23 **Core Curriculum: Pathology of the Heart.** Maurice Lev, FACC, and Jesse E. Edwards, FACC, directors. Palmer House, Chicago, Ill.

MAR. 25–27 **Electrocardiographic Interpretation of Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis.

MAR. 28–30 **High Blood Pressure—When and How To.** Robert S. Eliot, FACC, director. Gerald L. Wolf and Francis L. Land, co-directors. University of Nebraska Center for Continuing Education, Omaha.

APR. 1–10 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 4–6 **Advances in Clinical Cardiology.** Lawrence S. Cohen, FACC, director and Alfred L. Aronson, William W. L. Glenn, FACC, Allan V. N. Goodyer, FACC, Norman S. Talner, FACC and Steven Wolfson, FACC, co-directors. Yale University School of Medicine, New Haven, Conn.

APR. 17–19 **Core Curriculum—Vectorcardiography (A Basic Workshop).** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

APR. 22–25 **Current Concepts in Cardiology—1974.** Philip R. Akre, director and John A. Bowers and Masato Takahashi, FACC, co-directors. MGM Grand Hotel, Las Vegas, Nev.

MAY 6–9 **The Treatment of Coronary Syndromes.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 9–11 **The Ventricular Ectopic Beat: Heart-throb or Harbinger of Death.** Bernard Tabatznik and J. O'Neal Humphries, FACC, directors. Cross Keys Inn, Baltimore, Md.

MAY 15–17 **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director. Georgetown University School of Medicine, Washington, D. C.

MAY 17–19 **Core Curriculum: Rational Drug Therapy in Cardiovascular Disease.** Robert J. Lee, PhD., director. The Nassau Inn, Princeton, N. J.

MAY 23–25 **Cardiologist's Appraisal of Operable Heart Disease.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. St. Francis Hotel, San Francisco, Calif.

JUNE 6–8 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

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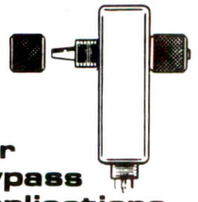

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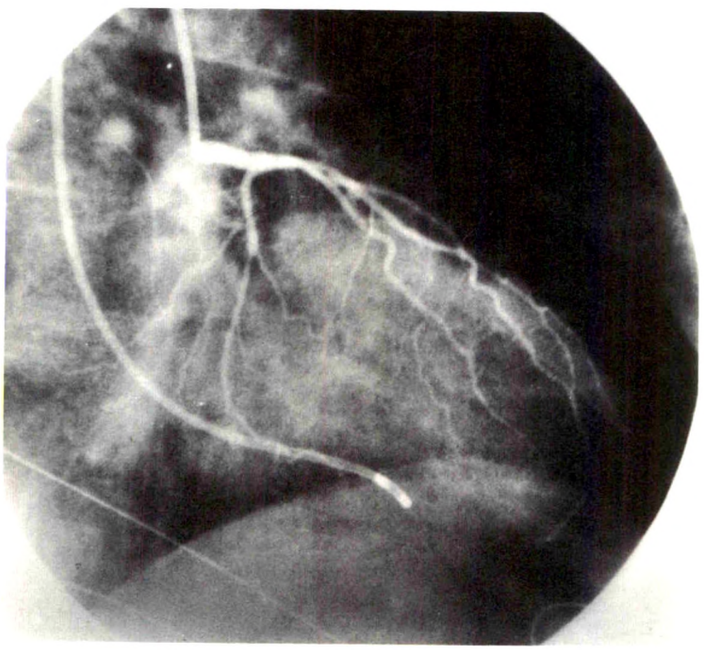

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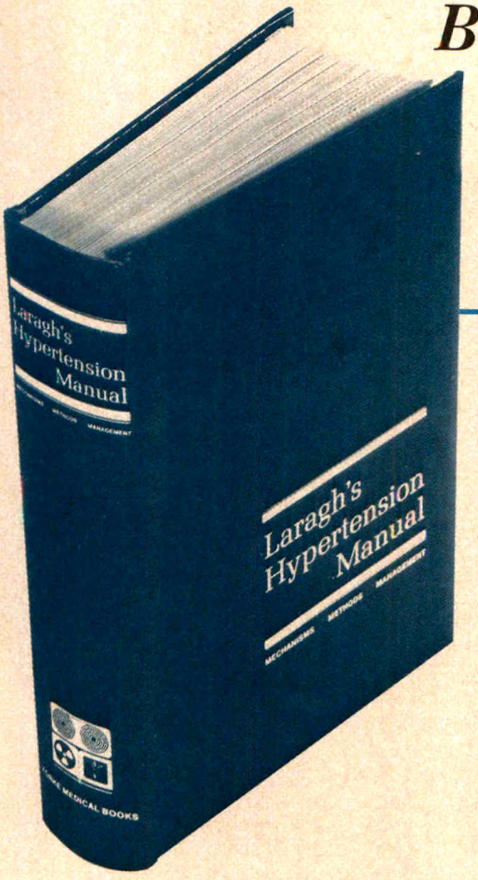

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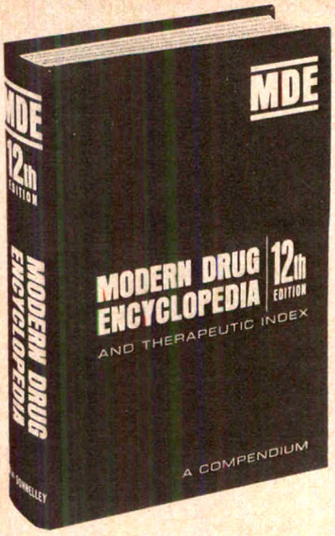

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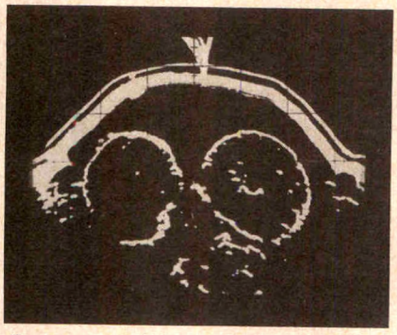

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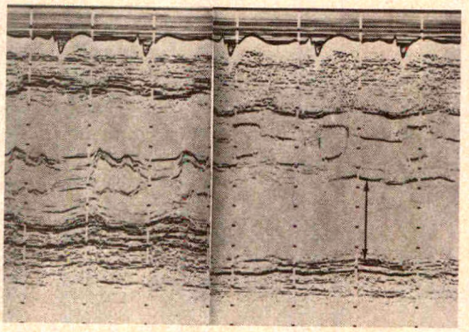
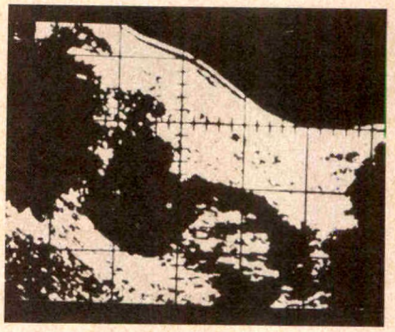
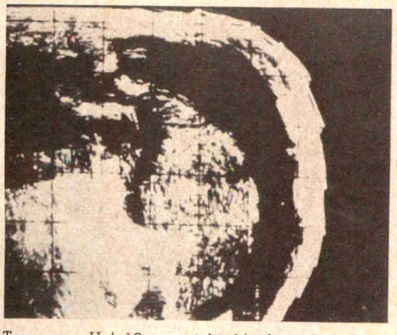


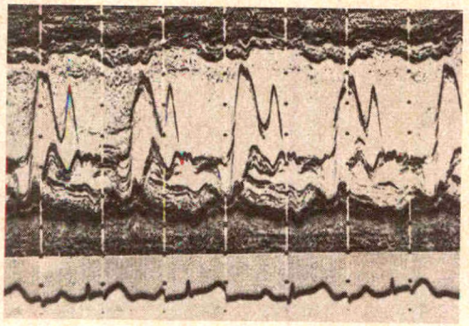
Patient with coronary artery disease and mitral regurgitation. Note enlarged left atrium (arrows). Photo courtesy Dr. Fred Winsberg, Montreal General Hospital, Montreal, Quebec, Canada



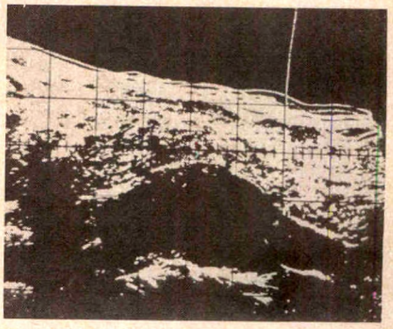
Longitudinal left kidney. (NOTE: 6cm upper pole renal cyst). Photo courtesy Dr. George Leopold, University of California, San Diego, CA.



Transverse U + 12cm vertebral body, right kidney, liver, ascites. (NOTE: cirrhotic liver separated from abdominal wall due to ascites). Courtesy Dr. George Leopold, Univ. of California, San Diego, CA.



Late systolic prolapse of posterior leaflet. Photo courtesy Dr. Fred Winsberg, Montreal General Hospital, Montreal, Quebec, Canada



Longitudinal L + 2cm aorta. (NOTE: aortic aneurysm measures 7.3cm). Photo courtesy Dr. George Leopold, University of California, San Diego, CA.

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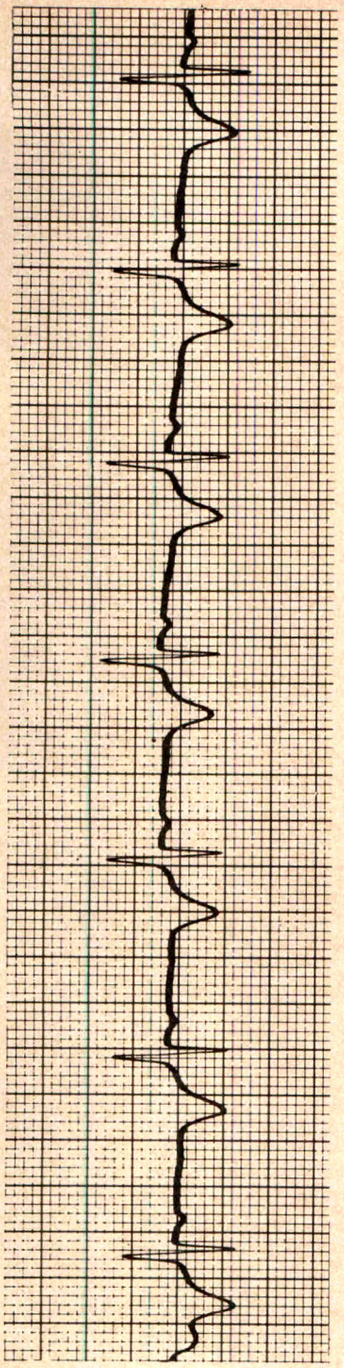

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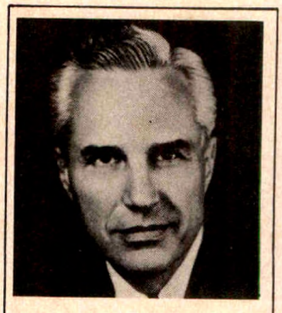

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- **Limit words as follows:** 100 to 250 words for major articles; 50 to 100 words for case reports.
- **Add at end of abstract:** an alphabetical list of 2 to 6 key words and subjects for indexing.

THE TEXT

- **Number pages** in sequence after abstract.
- **Type in duplicate;** double-space.
- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.

- **Cite in numerical** order every reference, figure and table. (Order of mention in text **determines the number** given to each.)
- **Place acknowledgments** at end of text, before references.

THE REFERENCES

- **Type in duplicate;** double-space.
- **Place immediately** after text, and number pages in sequence after text page numbers.
- **Number the references** in order in which they are mentioned in text.
- **Follow the general** arrangement, abbreviations and punctuation styles shown below.

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- **Start at top** of new page.
- **Type in duplicate;** double-space.
- **Number pages** in sequence after last page of references.
- **Identify** at the end of each legend and **in alphabetical order** all abbreviations in the figure described.

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- **Start each** table at top of new page.
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- **Give each table** a number (in roman numerals: Table I, II, etc.) and a title. Number the tables in order in which they are mentioned in the text.
- **Provide a footnote** to each table—identifying **in alphabetical order** all abbreviations used.

THE FIGURES

- **Submit 2 glossy prints** (not originals) of each photo and drawing.

Please note that art work of published articles will not be returned.

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(Author: please note that no periods are used after authors' initials.)

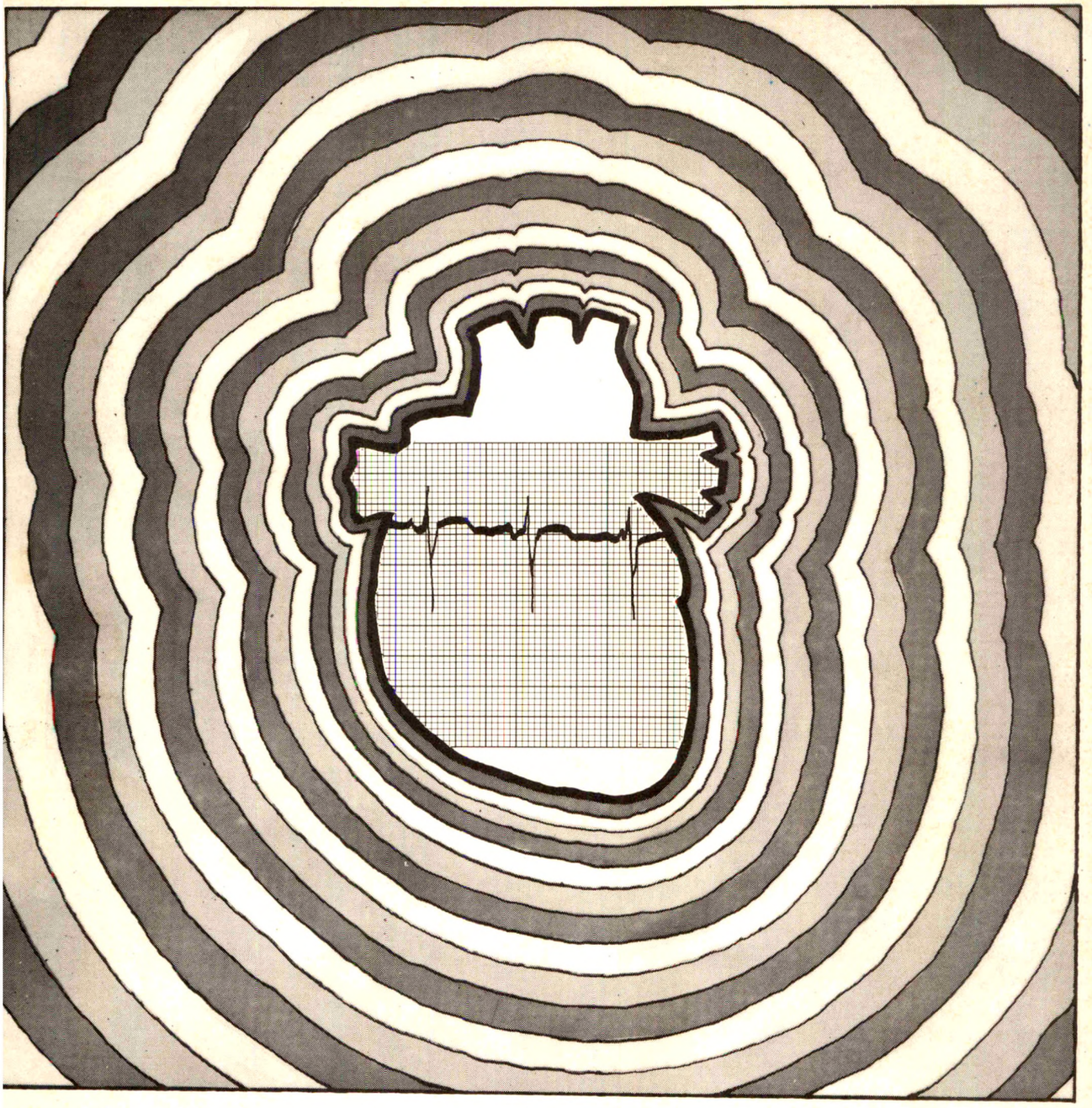
For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

(Author: all book references should have specific page numbers)



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"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

Kay Ciel® Elixir is potassium chloride... tastes good too!

COMPOSITION: Each 15 cc. (one tablespoonful) contains potassium chloride 1.5 Gm., supplying 20 mEq. of elemental potassium, in a cherry-flavored, palatable base, alcohol 4%. Contains no sugar.
INDICATIONS: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium or as a result of excessive vomiting and diarrhea.
CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
SIDE EFFECTS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
DOSAGE AND ADMINISTRATION: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
HOW SUPPLIED: One pint and one gallon bottles.

Cooper Cooper Laboratories, Inc., Wayne, N.J. 07470/Ste. Therese, P.Q., Canada

MARCH 1974

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Symposium on Effects of Surgical Treatment on the Natural History of Acquired Heart Disease
Part One: Coronary Artery Disease

John Ross, Jr., MD, FACC, Guest Editor

Contents on Page A9

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A YORKE MEDICAL JOURNAL

The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

while he's sleeping.

Quinaglute® Dura-Tabs® (quinidine gluconate) "a pharmacologic pacemaker":

- produces sustained serum quinidine levels, thus providing a convenient 8 or 12 hour dosage schedule
- usually insures uninterrupted therapeutic quinidine gluconate levels during sleep
- avoids peaks and valleys in plasma levels during which time the arrhythmias may recur
- maintains normal sinus rhythm following conversion by other techniques
- well tolerated to enhance patient cooperation — few G.I. disturbances

Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

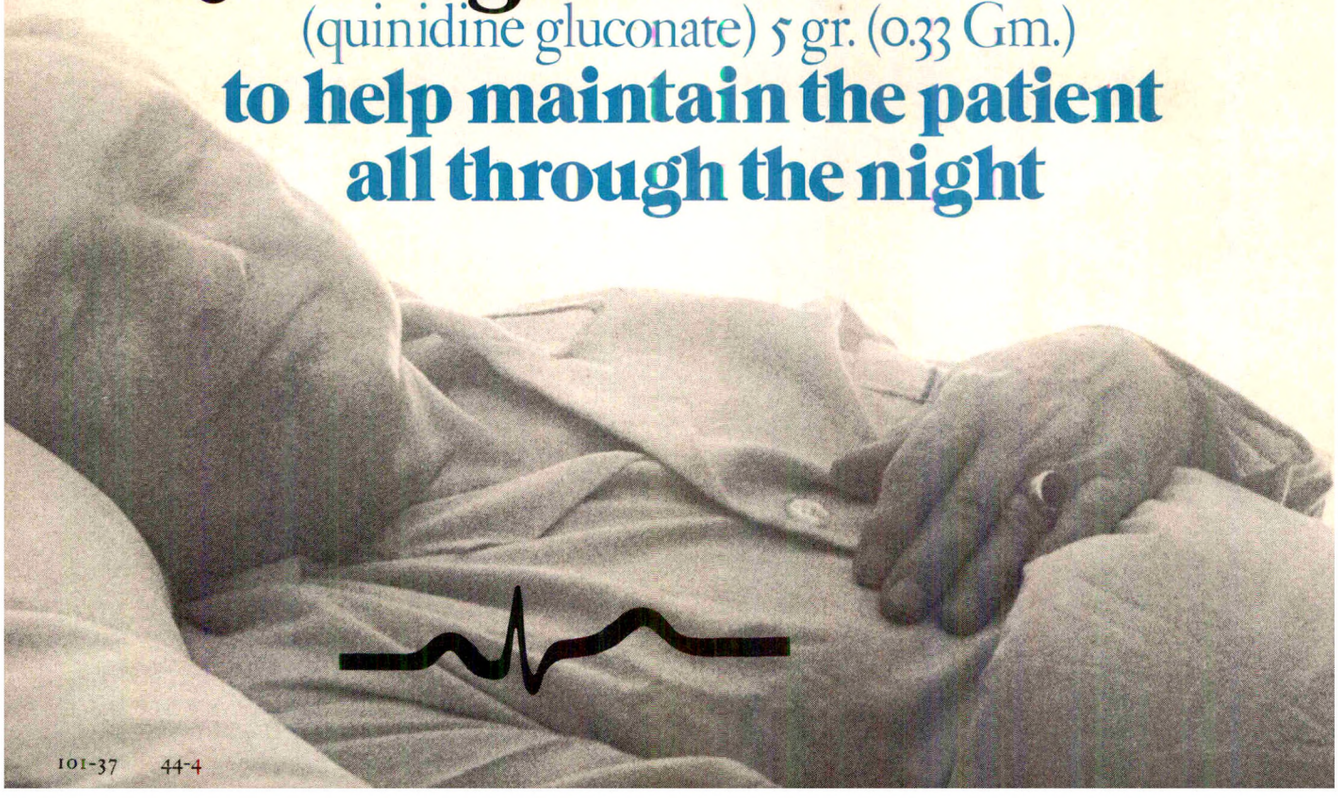
Before prescribing or administering, please refer to QUINAGLUTE full product information.

Cooper Laboratories, Inc.
Wayne, New Jersey 07470

Quinaglute® Dura-Tabs®

(quinidine gluconate) 5 gr. (0.33 Gm.)

to help maintain the patient all through the night



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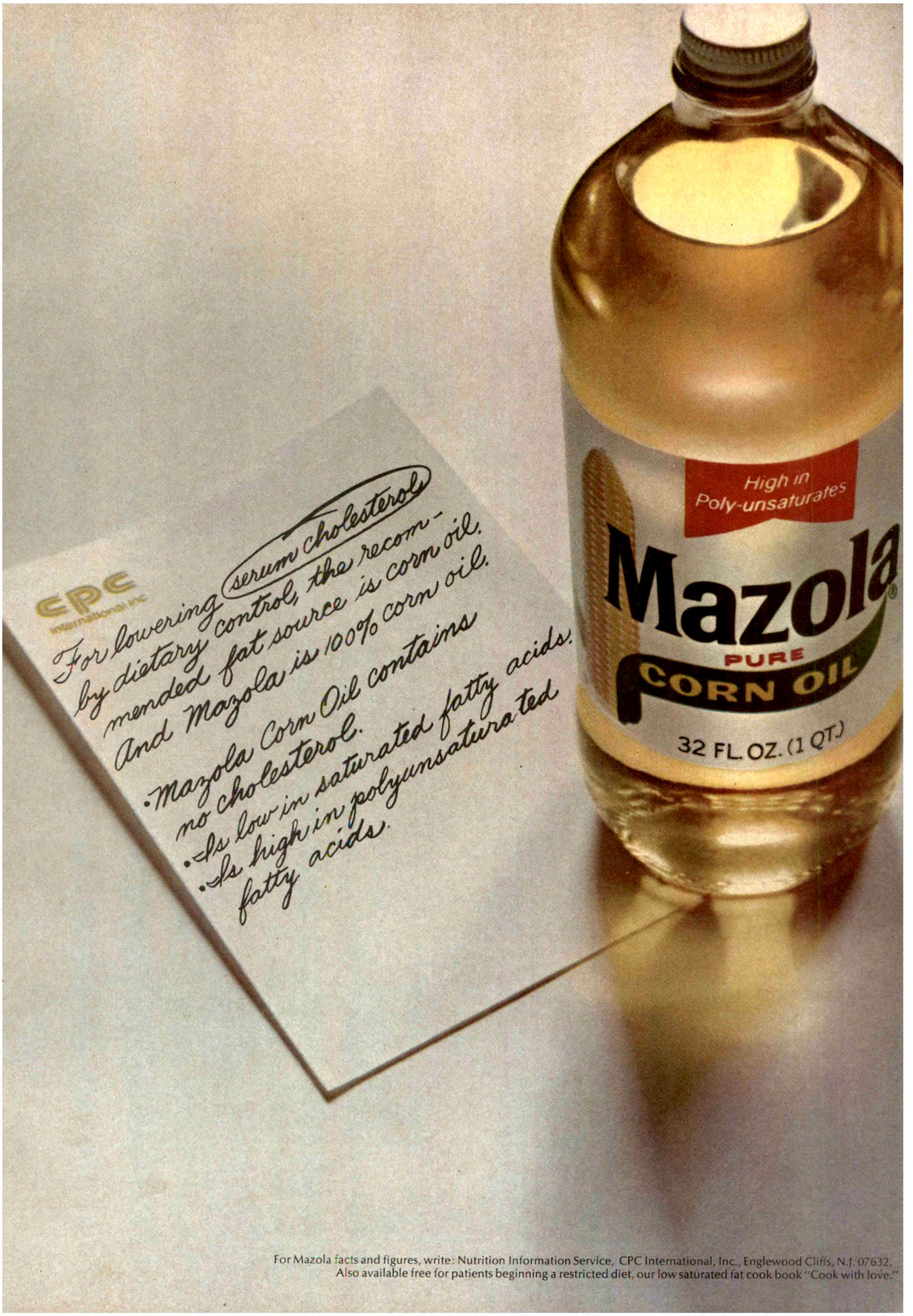
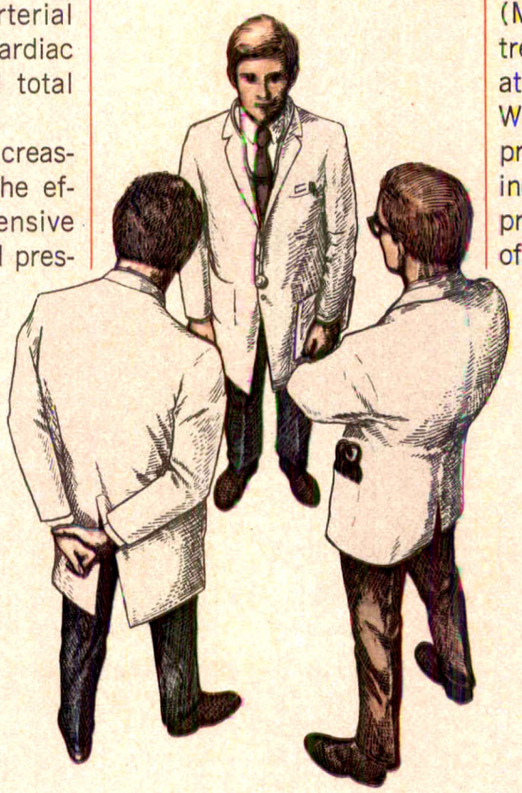


For Mazola facts and figures, write: Nutrition Information Service, CPC International, Inc., Englewood Cliffs, N.J. 07632.
Also available free for patients beginning a restricted diet, our low saturated fat cook book "Cook with love."

The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?

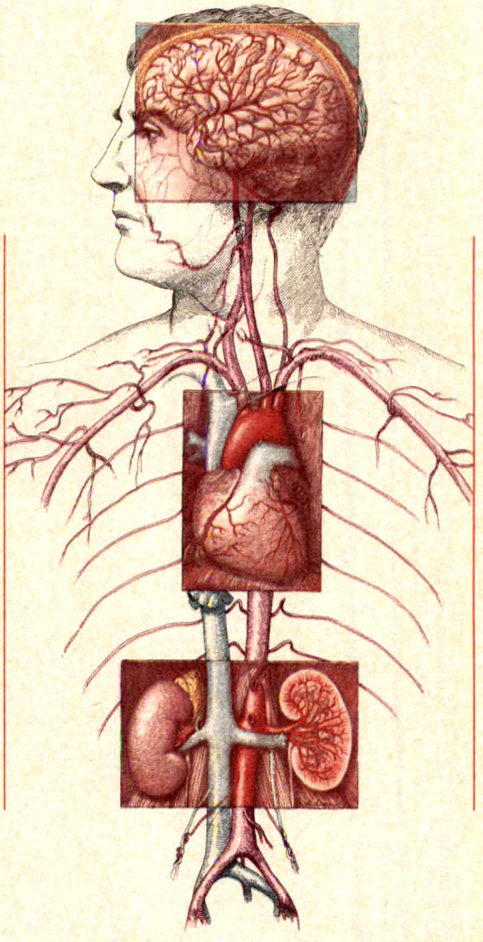


With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in

S. 8. 74

the more physicians rely on this unique antihypertensive



lowering blood pressure. But there are other considerations as well. Cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is actually slowed. Peripheral resistance is apparently reduced. ALDOMET does not usually compromise existing renal function; it generally does not reduce renal blood flow, glomerular filtration rate, or filtration fraction. And ALDOMET usually does not cause symptomatic postural or exercise hypotension.

Some patients on continuous methyldopa therapy may develop a positive direct Coombs test. For more details, see the brief summary of prescribing information.

Contraindicated in active hepatic disease and known sensitivity to the drug. Not recommended in pheochromocytoma or pregnancy. It should be used with caution in patients with a history of liver disease or dysfunction. Discontinue the drug if fever, abnormal liver function, jaundice, or acquired hemolytic anemia occurs.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®

(METHYLDOPA | MSD)

smoothly lowers blood pressure

For a brief summary of prescribing information, please see following page.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET® (METHYLDOPA | MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: Acquired hemolytic anemia has occurred rarely in association with therapy with methyldopa. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of the anemia. Rarely, however, fatalities have occurred.

Some patients on continued therapy with methyldopa develop a positive direct Coombs test; incidence reported has averaged between 10% and 20%. It rarely occurs in first six months of therapy, and if not seen within twelve months, is unlikely to develop with continued administration. Positive Coombs test is dose-related; lowest incidence occurs in patients on 1 g methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa. Prior knowledge of a positive Coombs reaction aids in evaluation of cross match for transfusions. Patients with positive Coombs tests at time of cross match may exhibit incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with blood otherwise compatible in the major cross match may be carried out. If positive, advisability of transfusion with blood compatible in major cross match should be determined by hematologist or expert in transfusion problems.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy in several patients with liver dysfunction has shown microscopic focal necrosis compatible with drug hypersensitivity. Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen; reversible agranulocytosis has been reported. Methyldopa may interfere with measurement of creatinine by alkaline picrate method and of uric acid by phosphotungstate method. When used with other antihypertensive drugs, potentiation of antihypertensive action may occur.

Usage in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Perform periodic hepatic function tests and white cell and differential blood counts during first six to twelve weeks of therapy or in unexplained fever. Discontinue if fever, abnormalities in liver function tests, or jaundice appears. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Discontinue drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Anesthetics requirements may be reduced; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension may occur after dialysis because methyldopa is removed by this procedure.

Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Do not exceed recommended daily dose of 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure, including dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency, are seen occasionally. Angina pectoris may be aggravated. Symptoms of orthostatic and exercise hypotension may occur; if symptoms occur, reduce dosage. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distension, constipation, flatus, and diarrhea occur occasionally; these can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently; if edema progresses or signs of pulmonary congestion appear, discontinue drug. Rarely, urine exposed to air may darken due to breakdown of methyldopa or its metabolites. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression, reversible thrombocytopenia, drug-related fever and abnormal liver function studies with jaundice and hepatocellular damage (see **Warnings** and **Precautions**), rise in BUN, and a single case of bilateral Bell's palsy.

Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

ADDENDUM

MSD MERCK SHARP & DOHME

Let's make blood pressure "required reading" for all physicians.

With recent estimates that about 23 million Americans have high blood pressure—and that half of them are not even aware of it—detection of the problem in asymptomatic persons has become an issue of national importance.

Family physicians are being urged to take blood pressure readings as a matter of office routine, regardless of the presenting complaint or the reason for the visit. And because many people do not see a family physician for relatively long periods of time, some experts are suggesting that ophthalmologists, gynecologists, dermatologists, orthopedists, psychiatrists, dentists, school nurses, family planning counselors, and other health-care personnel make blood pressure reading a routine part of every examination or consultation.

Of course, a diagnosis of hypertension cannot be made on the basis of a single reading, but routine blood pressure readings can uncover potential trouble in a certain proportion of patients. And when trouble is suggested, further evaluation can be pursued more effectively.

Blood pressure—"required reading" for all physicians.

The American Journal of CARDIOLOGY®

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The New Math of

It may increase diagnostic accuracy by an added 30%

If you're not testing for triglycerides, as well as for cholesterol, you may detect only 6 out of 10 patients with hyperlipidemia.[1]

If you're testing for <u>both</u> triglycerides and cholesterol, chances are you will detect more than 9 out of 10 patients (over 95%) with hyperlipidemia.[1]

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UP TO 35% REDUCTION OF ELEVATED CHOLESTEROL LEVELS

Cholesterol levels above 250 mg.% have decrease as much as 35%...and reductions up to 50% hav been reported.[2-5]

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10 YEARS OF SUCCESSFUL OVERALL CLINICAL EXPERIENCE

Reliable cholesterol- and triglyceride-lowering effec persists as long as treatment is uninterrupted.[2, Xanthomata may regress or disappear completely

ONE ATROMID-S CAPSULE FOUR TIMES A DAY

A simple, well-accepted regimen that patients ca stay with. Same dosage for *all* patients at *all* times

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID- (CLOFIBRATE). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON TH INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PRC THROMBIN LEVEL HAS BEEN STABILIZED.

Hyperlipidemia

of Atromid-S®

Brand of clofibrate

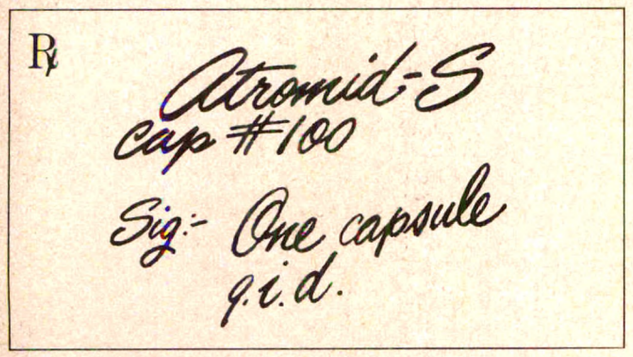
the most widely prescribed lipid-lowering agent–
significantly reduces
elevated levels of cholesterol and/or triglycerides,
not just cholesterol alone

Hyperlipidemia/**Atromid-S®** (clofibrate) **Ayerst®**

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)
helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone



BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. Hepatic biopsies are usually within normal limits. These effects are usually reversible when the drug is discontinued. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

The physician should monitor the patient with complete blood counts since peripheral anemia and, more frequently, leukopenia have been reported in patients who have been taking clofibrate. Whether these are drug-related is unknown.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus. There have been occasional cases of dry, brittle hair and of alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: increased angina, peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision.

DOSAGE AND ADMINISTRATION: Adult Dose: The recommended dosage for adults is one capsule (500 mg.) four times daily.

In Children: Insufficient studies have been done in children to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. 2. Gelfand, M. L., and Garber, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. 3. Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. 4. Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. 5. Levy, R. I., and Fredrickson, D. S.: Amer. J. Cardiol. *22*:576 (Oct.) 1968.

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ATROMID-S® (clofibrate) is available in the United States by arrangement with Imperial Chemical Industries Ltd.

The American Journal of CARDIOLOGY®

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363 **Early Sequential Changes in Left Ventricular Dimensions and Filling Pressure in Patients After Myocardial Infarction.** McKamy Smith, Robert A. Ratshin, Frank E. Harrell, Jr., Richard O. Russell, Jr. and Charles E. Rackley

370 **Left Ventricular A Wave Amplitude in Patients After Myocardial Infarction.** McKamy Smith, Richard O. Russell, Jr., Roger E. Moraski, Bolling J. Feild and Charles E. Rackley

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heartblock; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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MARCH 1974

The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 3

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CLINICAL STUDIES

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SUZANNE B. KNOEBEL, PAUL L. McHENRY, JOHN F. PHILLIPS and STEVEN WIDLANSKY

After intravenous administration of atropine sulfate (1 mg) heart rate and myocardial blood flow increased 52 and 48 percent, respectively, in 10 patients without coronary occlusive disease, 37 and 44 percent, respectively, in 14 patients with single vessel disease or partial occlusion of two vessels, and 30 and 15 percent, respectively, in 11 patients with two or three vessel disease. The latter group of 11 patients had a smaller increase in nutrient myocardial blood flow in response to atropine-induced cardioacceleration than patients with no or lesser degrees of coronary artery disease.

333 **Electrophysiologic Effects of Atropine on Atrioventricular Conduction Studied by His Bundle Electrogram**

MASOOD AKHTAR, ANTHONY N. DAMATO, ANTHONY R. CARACTA, WILLIAM P. BATSFORD, MARK E. JOSEPHSON and SUN H. LAU

Administration of atropine, 0.5 mg intravenously, produced an average increase of 20 percent in the sinus rate, enhanced atrioventricular (A–V) nodal conduction and shortened the functional and effective refractory periods of the A–V node without any direct effect on His-Purkinje conduction time or refractoriness. By shortening the functional refractory period of the A–V node, atropine shortened H_1–H_2 intervals on the His bundle electrograms.

344 **Effects of Digoxin on Atrioventricular Conduction Patterns in Man**

ANDREW C. PRZYBYLA, KARLEN L. PAULAY, EMANUEL STEIN and ANTHONY N. DAMATO

Bundle of His studies in 17 patients given digoxin demonstrated that an early atrial premature impulse was either blocked in the A–V node or reached the distal intraventricular conduction system so late that block or conduction delay below the His bundle observed in the control state was reduced or no longer occurred. These effects are attributed to the action of digoxin in slowing A–V nodal conduction of a premature impulse. Aberrant ventricular conduction in atrial fibrillation may thus be abolished.

351 **Diagnostic Value of Clinical History, Exercise Testing and Atrial Pacing in Patients with Chest Pain**

JAN PIESSENS, WALTER VAN MIEGHEM, HUGO KESTLELOOT and HILAIRE DE GEEST

In this study of 70 patients with a history of chest pain warranting coronary angiography, a clinical history of angina pectoris was a very sensitive (90 percent) but less specific (80 percent) predictor of severe coronary artery disease. Ischemic S–T segment depression of 1 mm or more was the most accurate electrocardiographic predictor. Atrial pacing was slightly more sensitive in provoking ischemic S–T segment depressions than the graded exercise test but showed less specificity and did not contribute significantly to diagnosis when a graded exercise test was performed.

Continued on page A13

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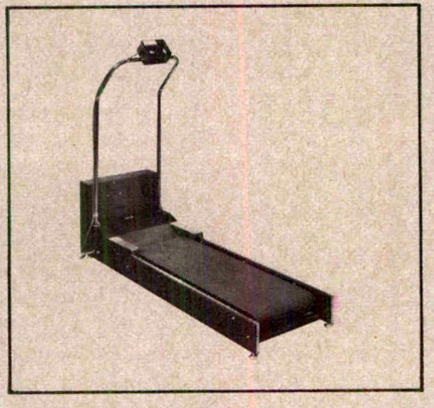

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357 Pulmonary Arterial Diastolic Pressure in Acute Myocardial Infarction

MICHAEL ROTMAN, JAMES T. T. CHEN, RONALD P. SENINGEN, JOHN HAWLEY, GALEN S. WAGNER, ROBERT M. DAVIDSON and MARCEL R. GILBERT

Pulmonary arterial diastolic pressure measurements provided a reliable estimate of left ventricular filling pressure and the degree of myocardial failure (third sound gallop or rales) in 91 patients with acute myocardial infarction. Radiographic evidence of increasing pulmonary congestion correlated significantly with the level of pulmonary arterial diastolic pressure.

363 Early Sequential Changes in Left Ventricular Dimensions and Filling Pressure in Patients After Myocardial Infarction

McKAMY SMITH, ROBERT A. RATSHIN, FRANK E. HARRELL, Jr., RICHARD O. RUSSELL, Jr. and CHARLES E. RACKLEY

In 14 patients studied within 8 days after acute myocardial infarction echocardiographic end-diastolic volume correlated with end-systolic volume and echocardiographic stroke volume but not with pulmonary arterial end-diastolic pressure. Large changes in the latter with no change in left ventricular end-diastolic dimension imply acute changes in left ventricular compliance. Early sequential changes in filling pressure, echocardiographic dimensions and left ventricular compliance correlated closely with the clinical course of the patients, suggesting the value of these data in the management of patients with hemodynamic instability after acute myocardial infarction.

370 Left Ventricular A Wave Amplitude in Patients After Myocardial Infarction

McKAMY SMITH, RICHARD O. RUSSELL, Jr., ROGER E. MORASKI, BOLLING J. FEILD and CHARLES E. RACKLEY

Increased left ventricular A wave amplitudes in 42 patients studied within 1 year after acute myocardial infarction indicated a decrease in both left ventricular diastolic compliance and systolic function. The inverse relation between left ventricular A wave amplitude and ejection fraction in this study suggests that augmentation of left ventricular end-diastolic fiber length by atrial systole may improve the performance of ventricles with decreased systolic function.

378 Dynamic Characterization of Premature Ventricular Beats and Ventricular Tachycardias

LESLIE M. EBER, BAROUH V. BERKOVITS, JACK M. MATLOFF, RICHARD GORLIN, with the technical assistance of JOHN M. COOKE

Premature ventricular beats and ventricular tachycardias produced in man during left ventriculography and in dogs by epicardial stimulation produced two similar patterns of ventricular contractions. Apically stimulated left ventricular beats produced an "hour glass" type of contraction pattern; basilar stimulation produced an inverse "teardrop" pattern. The former were hemodynamically more effective, thus indicating the importance of a normal sequence of ventricular contraction.

EXPERIMENTAL STUDIES

384 Surface Recording of Electrical Activity from the Region of the Bundle of His

NANCY C. FLOWERS, R. CHRIS HAND, PATRICIA C. ORANDER, CAREY B. MILLER, MARY O. WALDEN and LEO G. HORAN

Surface recordings of electrical activity during the P–R interval in 16 dogs are interpreted as having originated from the bundle of His in 7 dogs, from the region of the bundle branches in 6 and from both sites in 3. These results suggest that examination of the amplified surface P–R segment should become an important addition to the noninvasive techniques of cardiac evaluation.

Continued on page A15

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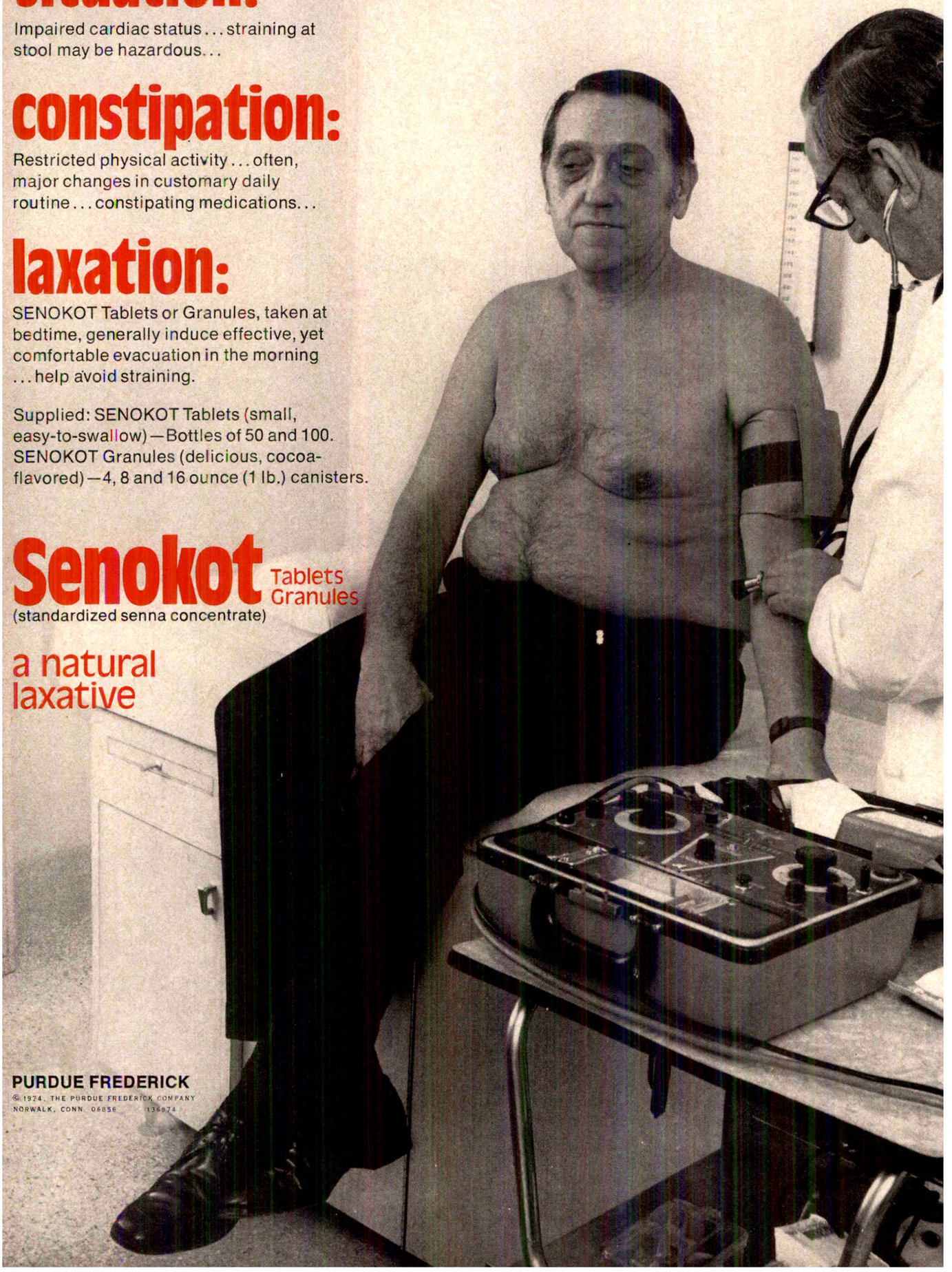

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390 Microelectrode Study of Wenckebach Periodicity in Canine Purkinje Fibers

JAMES R. WENNEMARK and JACK P. BANDURA

Experimentally produced Wenckebach periodicity appeared to be related to two factors: (1) a progressive decrease in the efficiency of the transmitted electrotonic potential arising from an increased maximal repolarization voltage of the transmembrane potential, and (2) a decreased diastolic interval that, in the presence of enhanced phase 4 diastolic depolarization, caused the voltage level from which the electrotonic potential originates to become further removed from the stimulation threshold with successive impulses of the cycle.

METHODS

399 Detection of Ventricular Arrhythmias in Real-Time with a Portable Analog Computer

DAVID S. CANNOM and DONALD C. HARRISON

This preliminary study of a portable analog computer to detect arrhythmias in 26 patients in a controlled in-hospital setting demonstrates the potential value of this device. Appropriate electrode placement is essential. Use of this detector may permit large-scale monitoring of patients with a high risk of sudden death, provided potential problems of long-term electrode placement, patient acceptance and tolerance of the concept of continuous monitoring and mechanisms for telephone transmissions to a coronary care unit or central hospital facility are solved.

PEDIATRIC CARDIOLOGY

403 Ventricular Septal Defect with Increased Pulmonary Vascular Resistance. Late Results of Surgical Closure

BEAT FRIEDLI, B. S. LANGFORD KIDD, WILLIAM T. MUSTARD and JOHN D. KEITH

Eighteen of 57 children died at or immediately after surgical closure of ventricular septal defect in the presence of increased pulmonary vascular resistance; seven late deaths occurred 1 to 7 years after operation. These overall results of surgery for ventricular septal defect and high pulmonary vascular resistance are unfavorable and call for surgical closure before age 2 years or pulmonary arterial banding in infancy before the development of significant pulmonary vascular obstructive changes.

410 Effect of Red Cell Volume Reduction on Pulmonary Blood Flow in Polycythemia of Cyanotic Congenital Heart Disease

AMNON ROSENTHAL and DONALD C. FYLER

Acute red cell volume reduction in patients with D-transposition of the great arteries and no significant pulmonary stenosis was associated with decreased pulmonary vascular resistance and increased pulmonary blood flow and mixing between the systemic and pulmonary circulations; in patients with severe pulmonary stenosis or atresia and a ventricular septal defect, it was associated with decreased pulmonary blood flow and left to right shunt and an increase in right to left shunt. These changes are attributed to a reduction in blood viscosity produced by lowering of hematocrit concentration.

Continued on page A17

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REPORTS ON THERAPY

415 Bypass Graft Surgery Versus Medical Therapy of Angina Pectoris

WILBERT S. ARONOW and EDWARD A. STEMMER

This carefully matched study of 20 patients with angina who underwent coronary artery bypass graft surgery and 20 similar subjects treated medically provides no good evidence that such surgery favorably alters the natural history of stable angina pectoris due to coronary artery disease by reducing mortality or preventing myocardial infarction. The operation may improve the quality of life and should be considered if medical therapy fails to relieve disabling angina.

SYMPOSIUM ON THE EFFECTS OF SURGICAL TREATMENT ON THE NATURAL HISTORY OF ACQUIRED HEART DISEASE. PART I. CORONARY ARTERY DISEASE

421 Introduction

JOHN ROSS, Jr.

423 Natural History of Angina Pectoris

T. JOSEPH REEVES, ALBERT OBERMAN, WILLIAM B. JONES and L. THOMAS SHEFFIELD

Combined data on patients with angina pectoris from several laboratories indicate an annual mortality rate of 2 percent when one coronary artery is significantly stenosed, 7 percent when two coronary arteries are stenosed and 11 percent when all three arteries are stenosed. These rates are increased when cardiac enlargement or congestive heart failure is also present. Such data on the natural history of angina pectoris are crucial in making a decision in surgical versus medical management of this condition.

431 Outlook for Patients After Coronary Artery Revascularization

VINCENT L. GOTT

Data from many centers indicate that about 85 percent of patients surviving the coronary artery bypass operation have relief of their angina and 60 percent have no further chest pain. Myocardial contractility for segments with a patent graft can be improved. The operative mortality rate for patients with stable angina, less than 6 percent in most centers, is related to the quality of ventricular function. The mortality rate in patients with unstable angina is considerably higher. Bypass surgery may favorably influence the annual survival rate in subjects with stable angina, but there are not enough data to say whether it can extend the life of patients with unstable angina.

DIAGNOSTIC SHELF

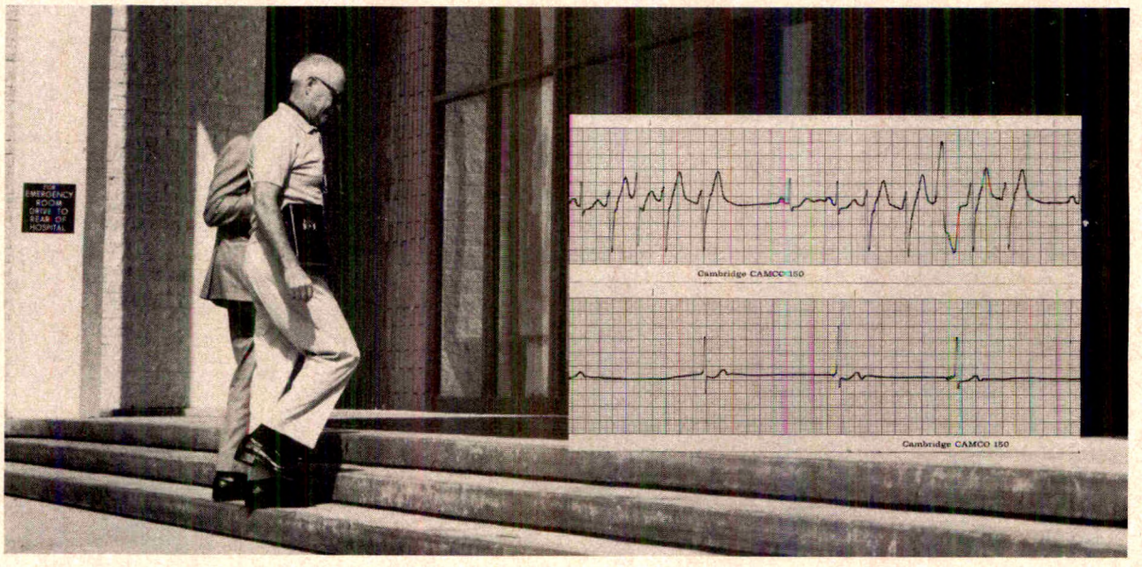
438 Echocardiographic Features of Primary Pulmonary Hypertension

DANIEL J. GOODMAN, DONALD C. HARRISON and RICHARD L. POPP

Echocardiograms in nine patients with primary pulmonary hypertension all showed a reduced diastolic slope of the anterior mitral valve leaflet motion simulating mitral stenosis but with normal motion of the posterior valve. The normal motion of this structure excludes the diagnosis of mitral stenosis as a cause for the pulmonary hypertension.

Continued on page A19

Holter DCG Monitoring Case History No. 20



A dynamic electrocardiogram was obtained on this 69-year old male patient, because of symptoms of severe dizziness and lightheadedness. The initial 1½ hours of the DCG demonstrated frequent 3-to-5 beat salvos of paroxysmal ventricular tachycardia and multifocal ventricular extrasystoles, which were frequently paired (see first strip); in addition, ventricular bigeminy and trigeminy were demonstrated. During the third hour of the recording (see second strip), a wandering pacemaker with an intermittent slow junctional rhythm (as low as 28 beats/minute) occurred.

While still wearing the Holter monitor, the patient was admitted to the hospital with symptoms of dizziness. The DCG permitted documentation of this patient's tachyarrhythmias and bradyarrhythmias, and appropriate therapy was then instituted.

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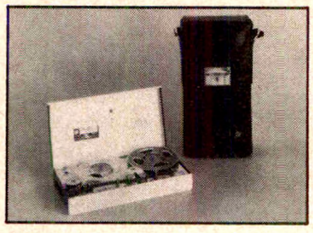

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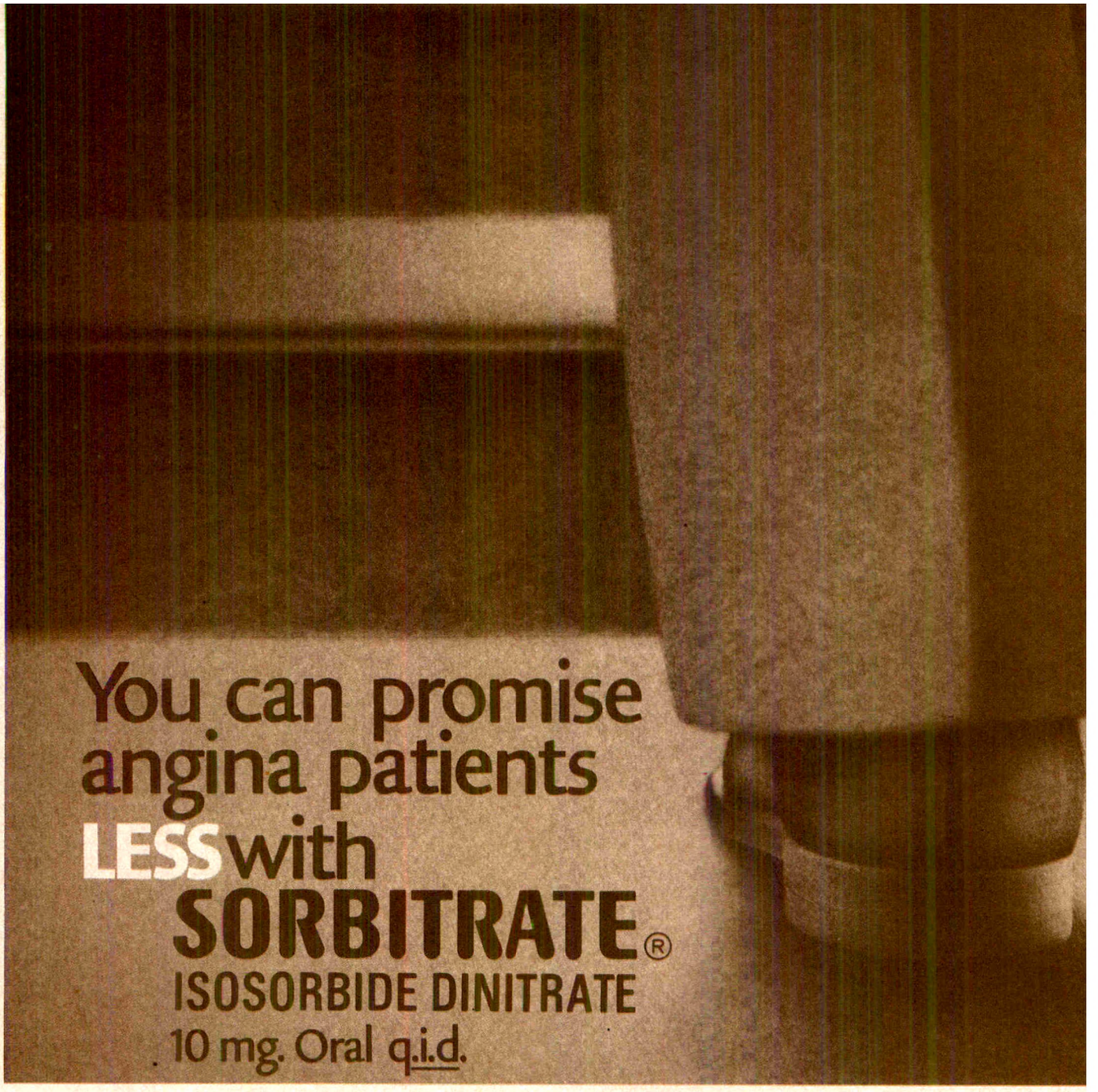

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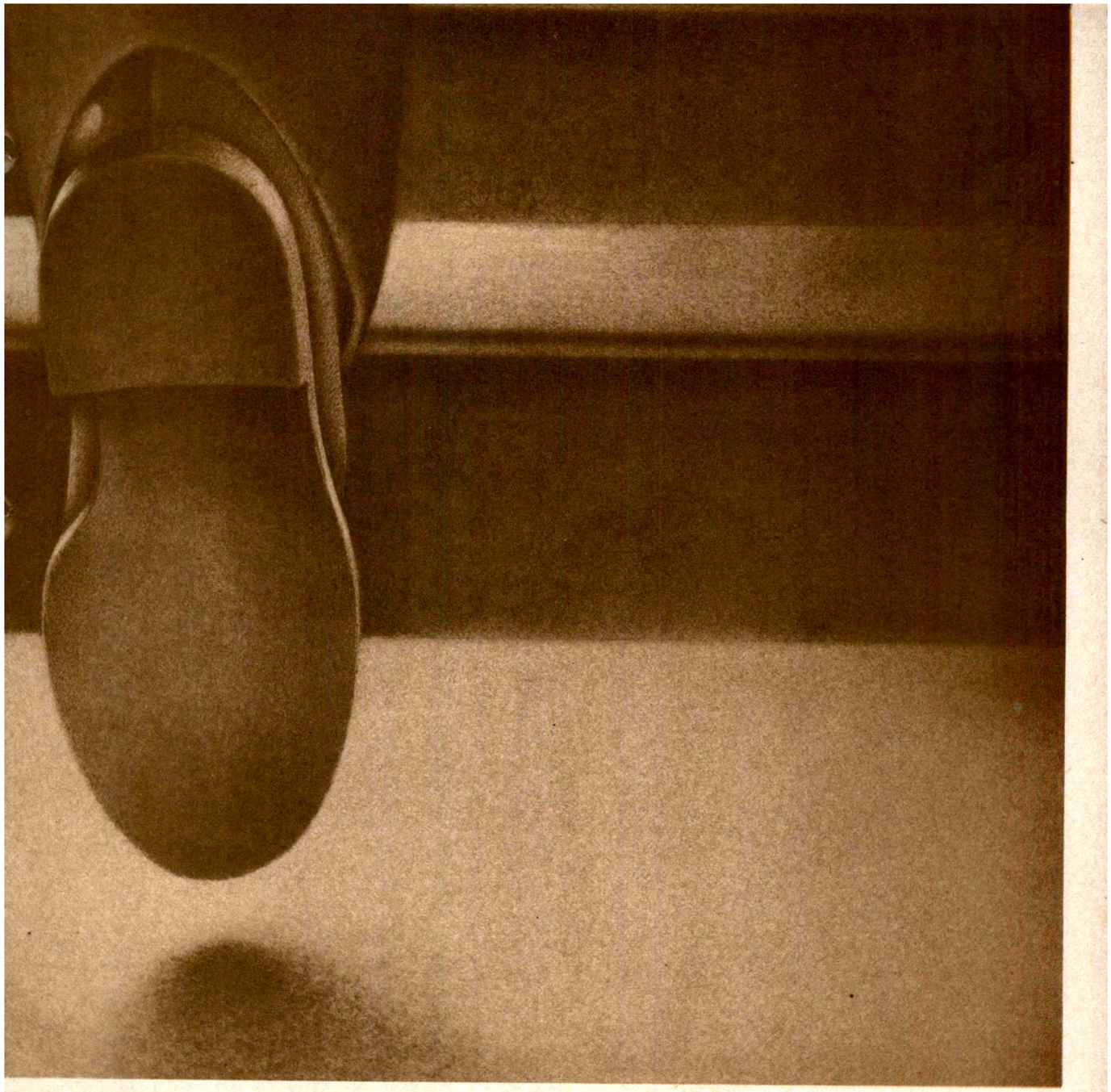
*Oral dosage forms of this drug have been evaluated as possibly effective. See Brief Summary.



SUMMARY OF PRESCRIBING INFORMATION

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For the treatment of angina pectoris.

Final classification of the less-than-effective indications require further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Oral tablets.

Individual Dose: Smallest effective dose should be employed. Five to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Oral SORBITRATE may be taken 3 to 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Oral: 15 to 30 minutes.

Duration of Effect: Oral: Estimated to be 4 to 6 hours.

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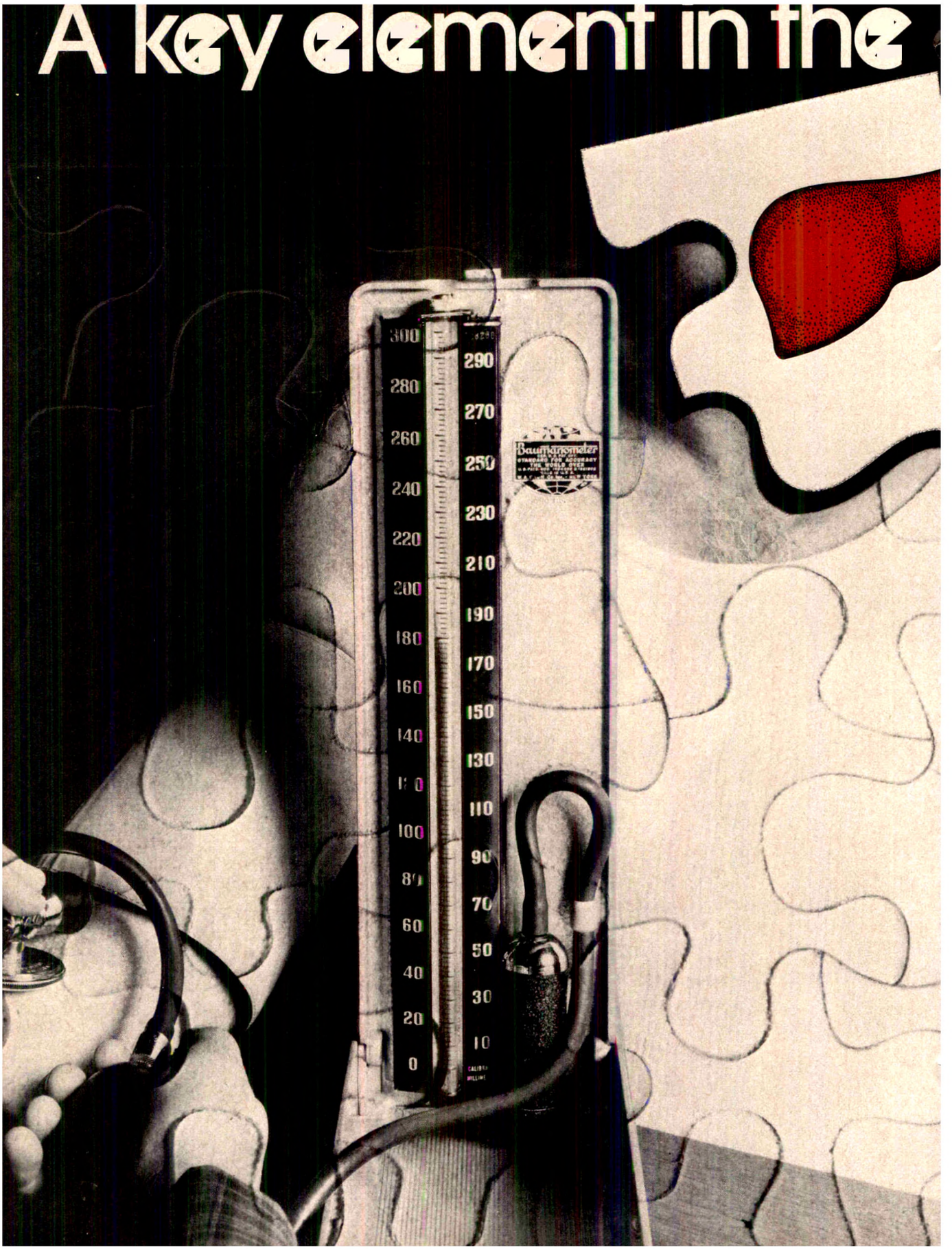
A key element in the



hypertension puzzle

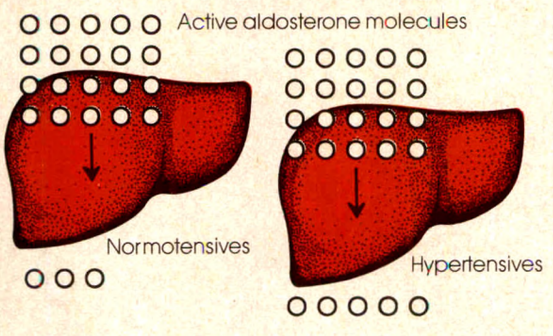
The liver metabolizes significantly less aldosterone in hypertensives than in normotensives.[1,2]

A significantly decreased hepatic MCR (metabolic clearance rate) of aldosterone, without significantly decreased SR (secretion rate), was demonstrated in approximately 90 percent of a group of 56 patients with benign essential hypertension.[1]

Thus "Failure of the aldosterone SR to fully adapt to the decrease in MCR may be responsible for a relative state of hyperaldosteronism in many patients with BEH [benign essential hypertension], even when the secretion and excretion rates are within normal range.

"It is conceivable that it is the mineralocorticoid [aldosterone] excess that is leading to an increase of sodium content in the arteriolar wall and the hypertensive process itself, in many patients with BEH."[2]

Metabolic clearance of aldosterone in hypertensives and in normotensives*



*Schematic representation

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

- Spironolactone blocks the pressor effect of aldosterone at the arteriole,[3-5] and exerts natriuretic action in the distal renal tubule.
- Hydrochlorothiazide exerts additive antihypertensive effect through its action at a different renal site.
- Aldactazide helps maintain potassium balance—without the need for potassium supplements—because the potassium-sparing action of spironolactone offsets the potassium-losing effect of hydrochlorothiazide.

References: 1. Genest, J., in Thorn, G. W., and Melby, J. C. (Editors): Aldosterone in Clinical Medicine, Medcom® Learning Systems, New York, Medical Communications, Inc., 1972, pp. 64-75.
2. Nowaczynski, W.; Kuchel, O., and Genest, J., in Genest, J., and Koiw, E. (Editors): Hypertension '72, Berlin, Springer-Verlag, 1972, pp. 244-255.
3. Crabbé, J.: Acta Endocrinol. (Kbh) 47:419-432 (Nov.) 1964.
4. Liddle, G. W.: Arch. Intern. Med. *102*:998-1004 (Dec.) 1958.
5. Liddle, G. W.: Ann. N.Y. Acad. Sci. *139*:466-470 (Nov. 22) 1966.

See following page for brief summary.

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

Indications—Hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusion may benefit from Aldactazide therapy.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of the renal function. Anuria; sensitivity to thiazides or other sulfonamide-derived drugs. Probably contraindicated in acute or severe hepatic failure.

Warnings—Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Potassium supplementation is recommended only in exceptional instances, but may be considered when a glucocorticoid is also given. Utilize normal dietary sources of potassium if possible when potassium supplementation is necessary. If enteric-coated potassium is used be alert to the possible development of hemorrhagic, stenotic, ulcerated or perforated small-bowel lesions; deaths have occurred. The possibility of exacerbation or activation of systemic lupus erythematosus by sulfonamide derivatives, including thiazides, has been reported.

Administer thiazides with caution to pregnant or lactating patients. Adverse reactions which may occur in the adult (hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, etc.) may possibly occur in the newborn, since thiazides cross the placental barrier and may also appear in breast milk.

Precautions—Consider the possibility of fluid and electrolyte imbalance. Serum and urine electrolyte determinations are particularly important in patients with excessive vomiting or in those receiving fluids parenterally. Medications such as digitalis may also influence serum electrolytes. Warning signs of possible fluid and electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains, cramps or fatigue, hypotension, oliguria, tachycardia, gastrointestinal symptoms. Hypokalemia may develop with brisk diuresis in severe cirrhosis or during the concomitant use of glucocorticoids or ACTH. Inadequate oral electrolyte intake contributes to hypokalemia. Hypokalemia may cause signs of digitalis intoxication with previously tolerated doses of digitalis.

Give Aldactazide cautiously to patients with severe liver disease since thiazides can precipitate hepatic coma; discontinue if mental confusion increases. Consider also other factors that may precipitate hepatic coma, including blood in the gastrointestinal tract or preexistent potassium depletion. Reversible elevation of NPN and BUN may occur in some patients receiving Aldactazide. The most common electrolyte disturbance is dilutional hyponatremia which requires appropriate corrective measures. A true low-salt syndrome is rare; discontinue Aldactazide and administer sodium for this condition.

Although rare, the most potentially serious electrolyte disturbance is hyperkalemia; if this occurs discontinue Aldactazide and restrict potassium intake. Rarely, fatality due to hyperkalemia has been reported. Hyperkalemia is more likely to occur in severely ill patients with relatively small urine output or in patients receiving supplemental potassium; determine serum electrolytes frequently in such patients. Consider the possibility of hyperuricemia or a decrease in tolerance to glucose.

Patients with severely resistant edema may have an increased diuretic response following the addition of a potent glucocorticoid, such as 15 to 20 mg. of prednisone daily, to Aldactazide therapy. Supplemental potassium will usually be necessary in such patients and the usual precautions with glucocorticoids are necessary. Use caution if regional or general anesthesia is necessary since Aldactazide reduces vascular responsiveness to norepinephrine in such patients. Thiazides may increase responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in patients who have undergone sympathectomy.

Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may increase serum PBI levels without signs of thyroid disturbance.

Adverse Reactions reported with *spironolactone* use: Drowsiness and lethargy, mental confusion, diarrhea and other gastrointestinal symptoms, mild androgenic manifestations (including hirsutism, menstrual irregularity, deepening of the voice), gynecomastia, inability to achieve or to maintain erection, headache, maculopapular or erythematous cutaneous eruptions, urticaria, drug fever, ataxia.

Adverse reactions reported with *thiazide* use: purpura, thrombocytopenia, leukopenia, agranulocytosis, gastrointestinal disorders (anorexia, nausea, vomiting, diarrhea, abdominal cramps), rash, pruritus, paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, urticaria, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness, restlessness. Reduce dosage or withdraw drug whenever adverse reactions are moderate or severe.

Dosage and Administration—Dosage should be determined by individual titration. *For essential hypertension* the daily *adult* dosage is two to four tablets in divided doses; continue treatment for two weeks or longer. Adjust the dosage according to the response of the patient. Reduce the dosage of other antihypertensive agents, particularly ganglionic blocking agents, by 50 percent since Aldactazide potentiates the action of such drugs. *For edema, ascites or effusion in adults* the average dosage is one tablet 4 times daily; dosage may range from 1 to 8 tablets daily in divided doses. The daily dosage of Aldactazide *in children* should provide 0.75 to 1.5 mg. of Aldactone® (spironolactone) per pound of body weight.

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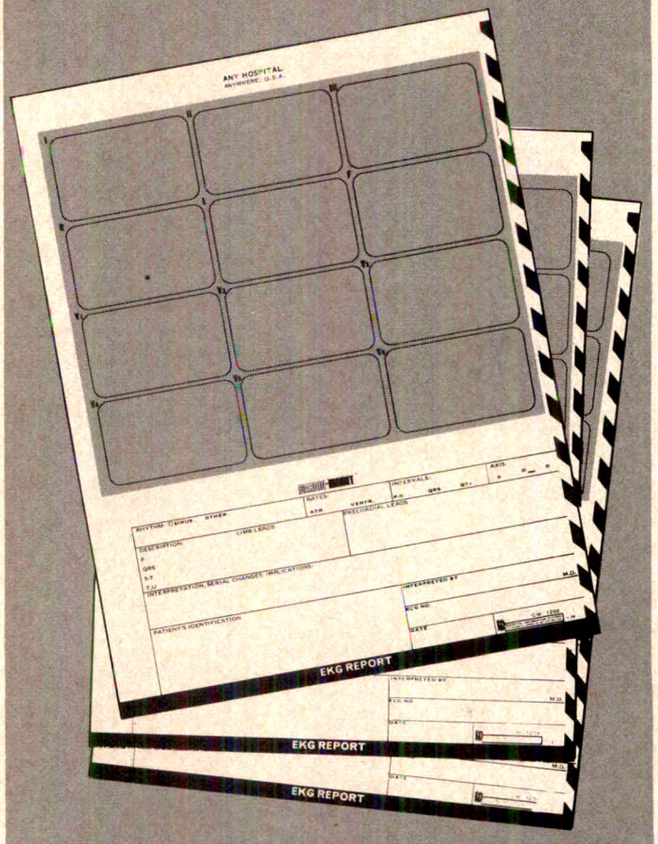

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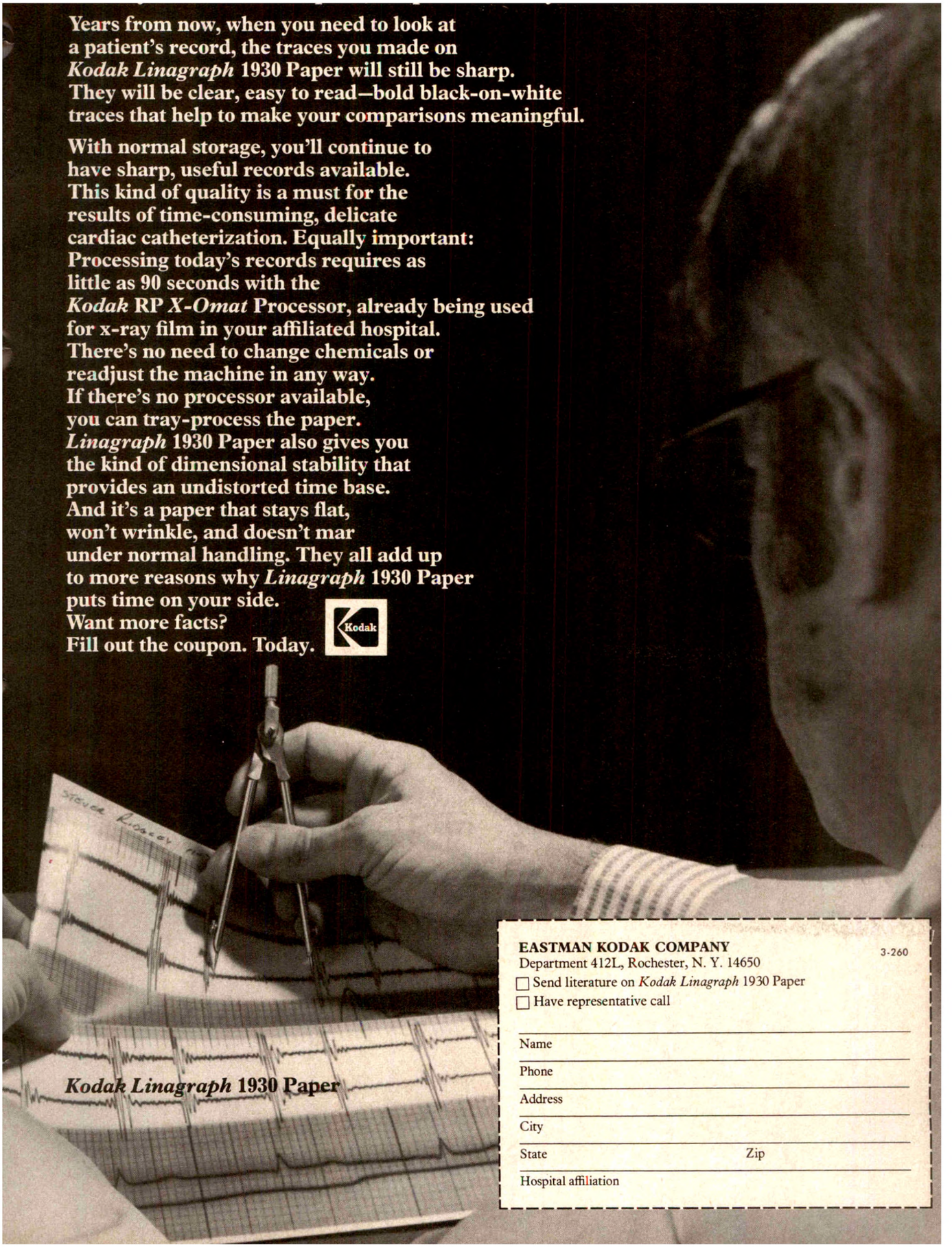

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By now she should

Rheumatic fever prevention and the noncompliant patient.

Patients on oral penicillin for prevention of recurrent rheumatic fever usually don't ignore their daily dosage regimen deliberately. But since patients are only human, doses *are* missed occasionally—through simple lapse of memory, lack of time or insufficient drug on hand.

Prolonged penicillin blood levels to obviate need for daily dosage.

A single injection of benzathine penicillin G (1.2 million units) once a month provides continuous prophylaxis in most patients. Which is why it's recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever.

A method of choice in treatment of strep pharyngitis, too.*

In therapy of mild to moderate Group A streptococcal pharyngitis without bacteremia, just one injection of 600,000 to 900,000 units usually maintains penicillin serum concentrations in children for the 10 days necessary to eradicate the infecting organisms.† In adults, 1.2 million units are required.

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

have taken all of them.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM benzathine penicillin G.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Benzathine Penicillin G Therapy is indicated as Prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with benzathine penicillin G has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma

Carefully avoid intravenous or intraarterial use or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

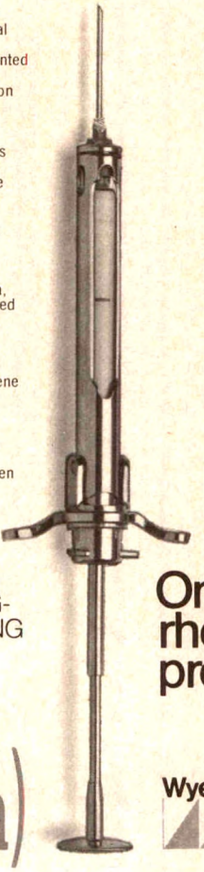
Composition: (units benzathine penicillin G as active ingredient): 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben and 0.14 mg. propylparaben.

600,000 units in 1-cc. TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

1,200,000 units in 2-cc. TUBEX, packages of 10, and in 2-cc. single-dose disposable syringe.

2,400,000 units in 4-cc. single-dose disposable syringe.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% povidone, 0.09% methylparaben and 0.01% propylparaben.



INJECTION

BICILLIN® LONG-ACTING

(sterile benzathine penicillin G suspension)

Once-a-month rheumatic fever prophylaxis.

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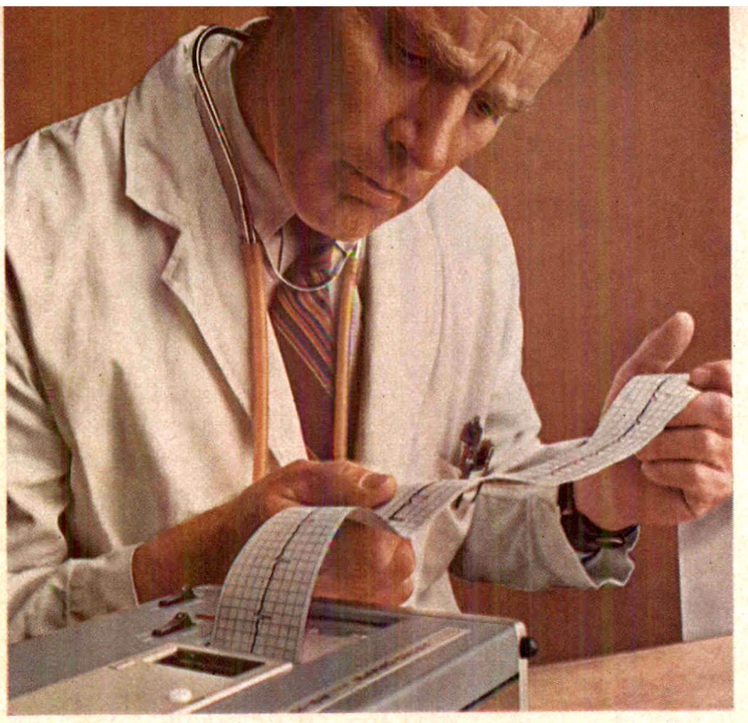
When cardiac complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on heart function

Excessive anxiety is one of a combination of factors that may trigger a series of maladaptive functional reactions which can generate further anxiety. Often involved in this vicious circle are some cardiac arrhythmias, paroxysmal supraventricular tachycardia and premature systoles. When these symptoms resemble those associated with actual organic disease, the overanxious patient needs reassurance that they have no

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

organic basis and that reduction of excessive anxiety and emotional overreaction would be medically beneficial.

The benefits of antianxiety therapy

Antianxiety medication, when used to complement counseling and reassurance, should be both effective and comparatively free from undesirable side effects. More than 13 years of extensive clinical experience has demonstrated that Librium (chlordiazepoxide HCl) fulfills these requirements with a high degree of consistency. Because of its wide margin of safety, Librium may generally be administered for extended periods, at the physician's discretion, without diminution of effect or need for increase in dosage. (See summary of prescribing information.) If cardiovascular drugs are necessary, Librium is used concomitantly whenever anxiety is a clinically significant factor. (See Precautions.) Librium should be discontinued when anxiety has been reduced to appropriate levels.

For relief of excessive anxiety adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

ROCHE

Roche Laboratories
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in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

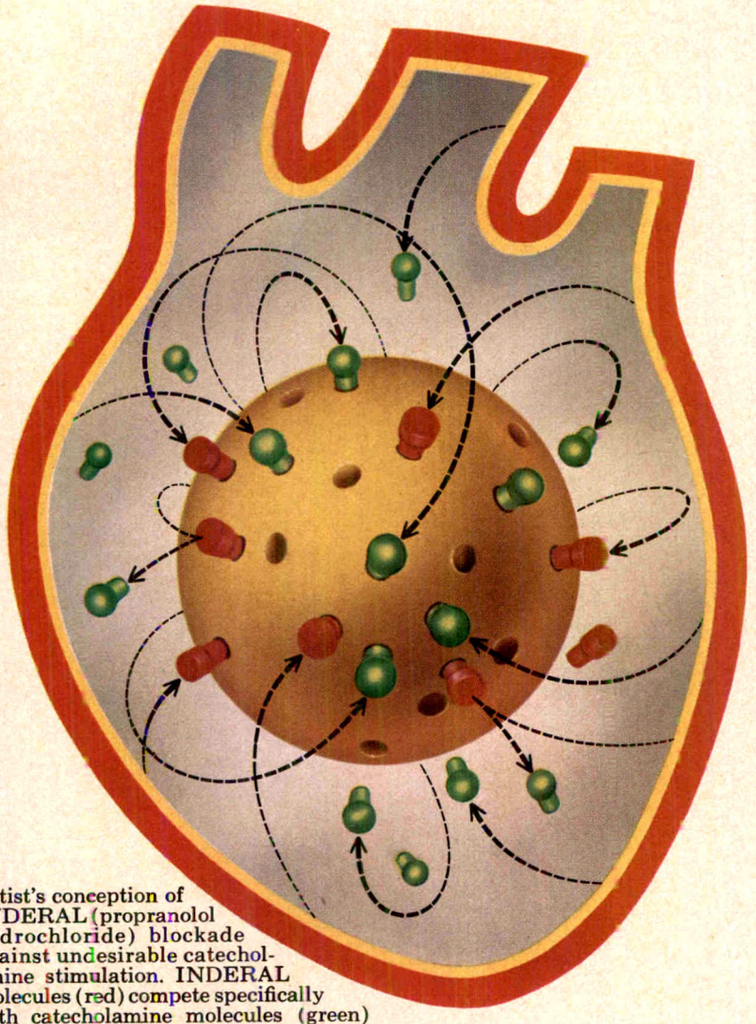
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

When the heart is under catecholamine siege

INDERAL® Brand of propranolol hydrochloride

The beta-adrenergic blocking agent for many cardiac arrhythmias



Artist's conception of INDERAL (propranolol hydrochloride) blockade against undesirable catecholamine stimulation. INDERAL molecules (red) compete specifically with catecholamine molecules (green) for available beta-receptor sites in cardiac tissue. With fewer catecholamine molecules gaining access to these sites, beta-adrenergic stimulation is reduced proportionately.

As the first beta-adrenergic blocking agent in clinical cardiologic use, INDERAL (propranolol hydrochloride) helps prevent or control catecholamine-induced supraventricular cardiac arrhythmias by means of a unique mechanism of action.

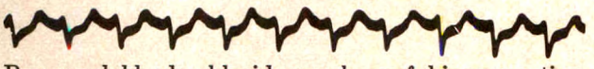
Excitatory adrenergic activity from sympathetic nerve endings and the adrenal medulla is mediated in myocardial and pacemaker tissue via beta receptors. Through blockade of undesirable catecholamine stimulation at these sites, INDERAL decreases impulse formation and conduction, and thus the rate and force of myocardial contraction. The clinical benefit is generally a reduction of supraventricular rate, a slowing of ventricular response, and restoration to sinus rhythm in many cases. In responsive patients, a subsequent maintenance regimen of 10 to 30 mg. INDERAL three or four times daily can prevent recurrence or reduce the frequency and severity of paroxysmal attacks.

With its unique site of action, INDERAL does not interfere with the therapeutic actions of nonadrenergic cardiotonic agents. Thus INDERAL can be used in combination—or alone—to control arrhythmias when other drugs have failed to produce a satisfactory response.

INDERAL is especially effective in the management of catecholamine-induced supraventricular arrhythmias. The response of ventricular arrhythmias is generally less predictable. INDERAL has proved to be of particular value in the control of digitalis-induced arrhythmias.

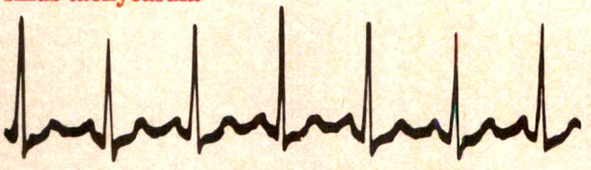
Proved effective over 6 years' clinical use

paroxysmal atrial tachycardia[1-8]



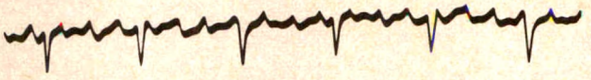
Propranolol hydrochloride may be useful in preventing recurrent attacks of paroxysmal atrial tachycardia "including attacks which may be a part of the Wolff-Parkinson-White syndrome."[1]

sinus tachycardia[9]



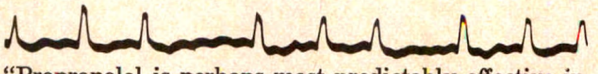
Sonnenblick "would use propranolol hydrochloride in treating a rapid sinus tachycardia which is poorly tolerated by the circulation—if the tachycardia were not due to some underlying process such as occult blood loss."[9]

atrial flutter[4-6,8-11]



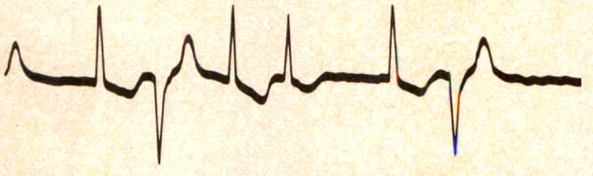
"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not being controlled by digitalis, especially in the presence of mitral valve disease."[9]

atrial fibrillation[1,3-10]



"Propranolol is perhaps most predictably effective in the treatment of patients with atrial fibrillation. It reduces the ventricular rate by prolonging the functional refractory period of the atrioventricular node. This occurs whether or not the patient is receiving digitalis."[3]

arrhythmias of digitalis intoxication[1,3-6,8-10]



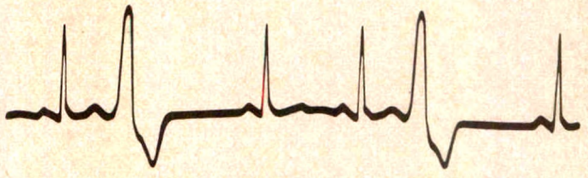
"Propranolol has been especially useful in treating patients with arrhythmias in the presence of established or suspected digitalis toxicity. All too common is the clinical situation in which we know the patient has had digitalis, but do not know whether he is toxic to digitalis. Propranolol may be a very useful drug in this situation."[1]

According to Wehrmacher, propranolol hydrochloride "is probably the treatment of choice for digitalis-induced tachyarrhythmias."[10]

ventricular tachycardias (when a matter of minutes in controlling the arrhythmia may mean life or death and when cardioversion technics are not available)[3,4,7,9,10,12]

"There appears to be a special place for the use of propranolol in patients with prolonged cardiac arrest associated with resistant, recurrent ventricular fibrillation. Propranolol has been shown to have an anti-fibrillatory effect, and we [the clinicians] believe it should be used when standard resuscitation methods and drugs have not produced a satisfactory cardiac rhythm."[12]

arrhythmias associated with anesthesia in selected cases[3,10,12-15]



In the treatment of cardiac disturbances occurring during and/or following halothane anesthesia for cardiovascular operations, 141 episodes in 115 patients "responded consistently to 1 to 2 mg. of propranolol intravenously without serious side effects. The onset of the drug's action was apparent within one to three minutes after its injection."[13]

Also recommended in the management of hypertrophic subaortic stenosis...[5,10,16]

Oral administration has produced symptomatic improvement in a large majority of patients, some treated for several days, and others for as long as several months.[10]

...and pheochromocytoma[3,6,8,10,17,18]

"When surgical removal [of the tumor in pheochromocytoma] is impossible, administration of both α- and β-adrenergic blocking drugs is essential for long-term control."[10]

Administered with awareness of the Contraindications, Warnings, Precautions, and Adverse Reactions, INDERAL (propranolol hydrochloride) provides a valuable tool in controlling a wide variety of cardiac arrhythmias, including cases that have proved refractory to previous therapy with other drugs.

With judicious use of INDERAL in suitably selected patients, symptomatic improvement is most frequently obtained; restoration to sinus rhythm is often possible.

References: 1. Aagard, G.N.: Northwest Med. *70*:47 (Jan.) 1971. 2. Gettes, L.S., and Yoshonis, K.F.: Circulation *41*:689 (Apr.) 1970. 3. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 4. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 5. Stampfer, M., and Epstein, S.E.: J.S. Carolina Med. Assoc. *65*:249 (July) 1969. 6. Theilen, E.O., and Wilson, W.R.: Med. Clin. N. Amer. *52*:1017 (Sept.) 1968. 7. Frieden, J., *et al.*: Am. J. Cardiol. *22*:711 (Nov.) 1968. 8. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 9. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971. 10. Wehrmacher, W.H.: Curr. Med. Dig. *35*:1031 (Oct.) 1968. 11. Richardson, D.W.: Int. Med. Dig. *86*:26 (July) 1970. 12. Slomon, G.: Br. Med. J. *4*:508 (Dec. 2) 1967. 13. McClish, A., *et al.*: Can. Med. Assoc. J. *99*:388 (Sept. 7) 1968. 14. Bird, C.G., *et al.*: Anaesthesia *24*:180, 1969. 15. Ikezono, E., *et al.*: Anesth. Analg. (Current Researches) *48*:598 (July-Aug.) 1969. 16. Belz, G.G.: Med. Klin. *64*:2019, 1969. 17. Engelman, K.: Hosp. Med. *6*:112 (May) 1970. 18. Crout, J.R., and Brown, B.R., Jr.: Anesthesiology *30*:29 (Jan.) 1969.

BETA-BLOCKADE / **INDERAL**® (propranolol hydrochloride)

Ayerst®

(See last page of advertisement for prescribing information.)

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL®
(propranolol hydrochloride)

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS

Cardiac Arrhythmias
1) Supraventricular arrhythmias
a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)
b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.
c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)
d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.
2) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.
a) Ventricular tachycardias
With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*
b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.
3) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)
Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)
4) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)
Hypertrophic Subaortic Stenosis
INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.
Pheochromocytoma
After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.
It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.
In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.
With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.
IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.
IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.
IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.
IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL (propranolol hydrochloride) should be titrated carefully when administered for arrhythmias occurring during anesthesia.
IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.
IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.
DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.
USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.
In chronically treated patients, dosage should be gradually reduced over a two week period when it is anticipated that the administration of INDERAL will be discontinued. There have been a few reports of myocardial infarction occurring within 2-3 days of propranolol hydrochloride discontinuation in angina pectoris patients, but an association has not yet been established.
As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura
Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics
Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation
Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress
Respiratory: bronchospasm
Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Miscellaneous: reversible alopecia
Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The oral route of administration is preferred.
ORAL
ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.
HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.
PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg. daily in divided doses.
PEDIATRIC DOSAGE
At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.
INTRAVENOUS
Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.
Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:
BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY
CARDIAC FAILURE—DIGITALIZATION AND DIURETICS
HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)
BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS—No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.
No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.
INJECTABLE—No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst AYERST LABORATORIES
NEW YORK, N.Y. 10017

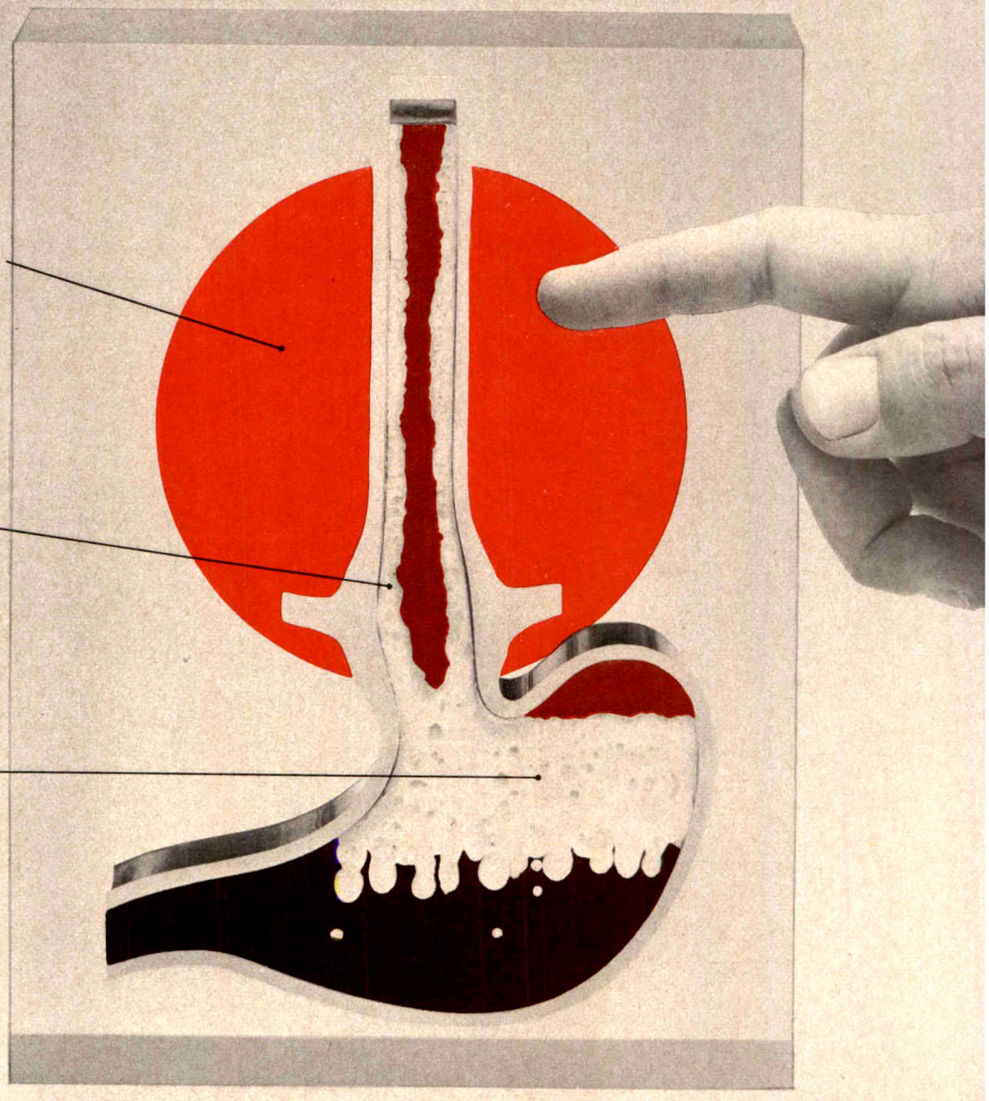
INDERAL® (propranolol hydrochloride) is available in the United States by arrangement with Imperial Chemical Industries Ltd. 7349

"This is the real Heartburn Zone
This is where GAVISCON® works

The Real Heartburn Zone
When gastric juice refluxes into the esophagus, stomach contents irritate sensitive nerve endings in esophageal mucosa to produce the pain of heartburn.

Gaviscon Coats
The Gaviscon foam coating clings to esophageal mucosa for pinpoint neutralization of gastric contents which might reflux from the stomach.

Gaviscon Floats
In the cardia and fundus of the stomach, GAVISCON® FOAMTAB® tablets form a soft, viscous layer of floating antacid foam that precedes gastric contents refluxing into the esophagus.



GAVISCON®

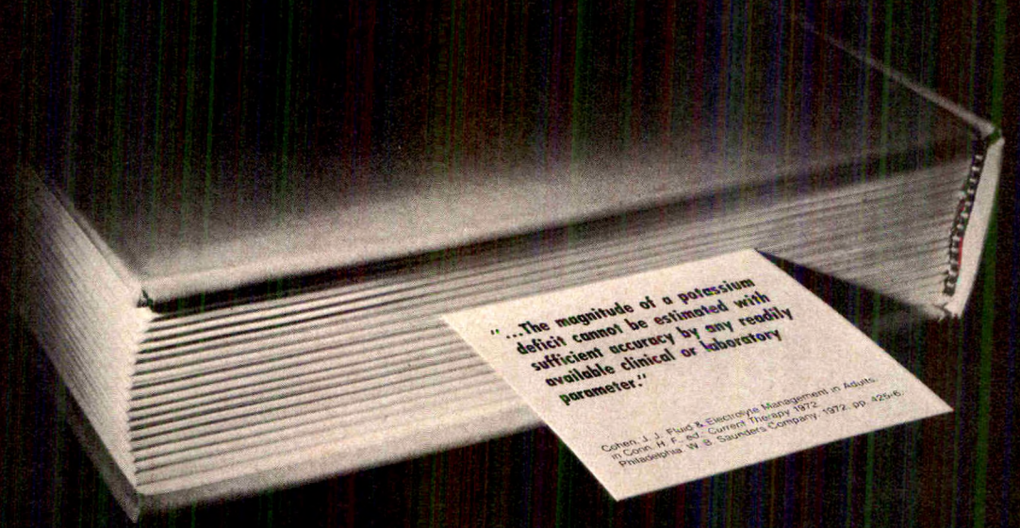
FOAMTAB®

(Alginic acid, 200 mg; aluminum hydroxide dried gel, 80 mg; magnesium trisilicate, 20 mg; sodium bicarbonate, 70 mg)
CHEWABLE ANTACID TABLETS for relief of heartburn accompanying hiatal hernia, gastroesophageal reflux, and esophagitis.

Another patient benefit product from PHARMACEUTICAL DIVISION MARION LABORATORIES, INC. KANSAS CITY, MISSOURI 64137

elp prevent this common thiazide and furosemide problem:

HIDDEN HYPOKALEMIA



rescribe good-tasting

KLORVESS®

effervescent tablets

ch tablet contains 20 mEq. each of potassium and chloride supplied by potassium loride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g.

1 ratio K^+ and Cl^- in solution

IMPLE TO TAKE—Tablets dissolve in 3-4 oz. cold water

PARKLING TASTE APPEAL—Fruitlike flavor

ATIENT ACCEPTANCE—Reduces chance of G.I. irritation. No added calories.

NIT DOSE CONVENIENCE—Tablets individually foil-wrapped

LORVESS offers what you and the patient like

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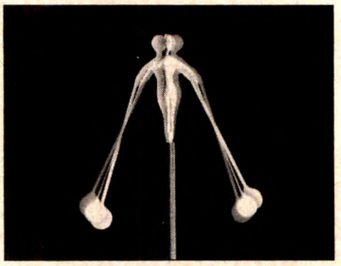

KLORVESS®
Effervescent Tablets

Description: Each dry effervescent tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g. Solution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate, and l-lysine hydrochloride.

Indications: For prevention or correction of potassium depletion and hypokalemic alkalosis. Especially useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each tablet completely in the stated amount of water.

Adverse Reactions: Vomiting, diarrhea, nausea and abdominal discomfort may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, and tall, peaked T waves.

Dosage and Administration: Adults: 1 tablet (20 mEq. each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water 2 to 4 times daily depending upon the requirements of the patient. The approximate minimum adult daily requirement of potassium is 40 mEq. Deviations from this recommendation may be indicated, since no average total daily dose can be defined but must be governed by close observation for clinical effects.
NOTE: Klorvess should be taken with meals.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

How Supplied: Klorvess Tablets (white, round) in boxes of 60 (2 Rx units of 30, NDC 43-100-87). Each tablet is individually foil wrapped.

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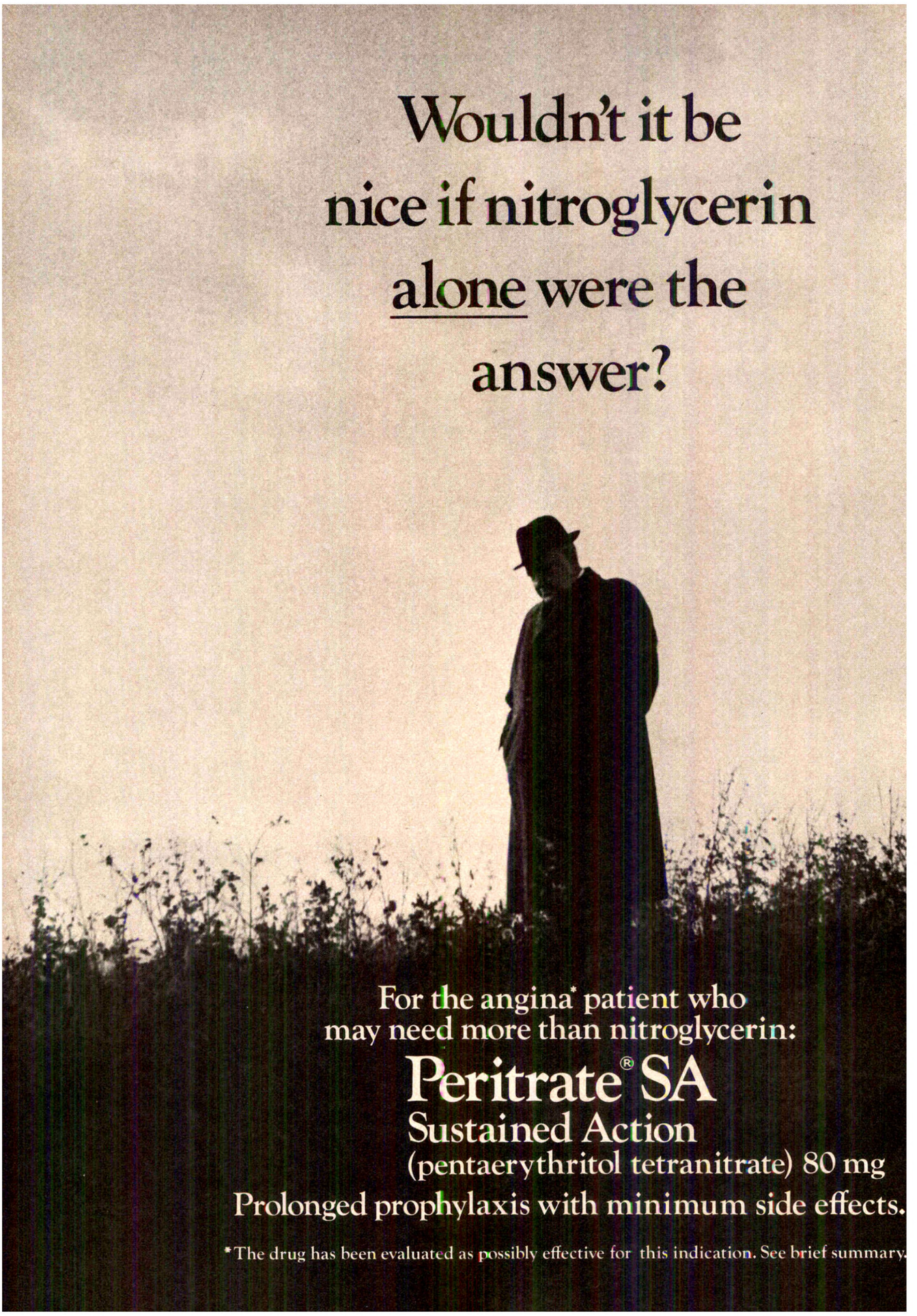
Wouldn't it be nice if nitroglycerin alone were the answer?



For the angina* patient who may need more than nitroglycerin:

Peritrate® SA

Sustained Action

(pentaerythritol tetranitrate) 80 mg

Prolonged prophylaxis with minimum side effects.

*The drug has been evaluated as possibly effective for this indication. See brief summary.

Peritrate® SA

Sustained Action
(pentaerythritol tetranitrate) 80 mg

CAUTION: Federal law prohibits dispensing without prescription.

Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 and 1000.

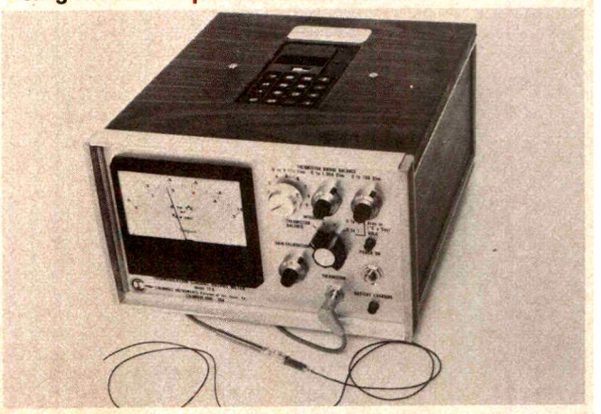
Additional Dosage Forms: Peritrate 20 mg–light green, scored tablets; Peritrate 10 mg–light green, unscored tablets. Bottles of 100 and 1000. Full information is available on request.

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950

PE-GP-41

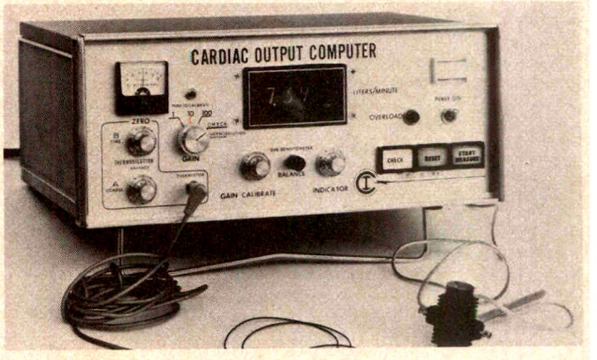
THERMODILUTION

Using room temperature indicator!



THERMODILUTION CARDIAC OUTPUT METER AND INTEGRATOR

- An intermediate instrument between the simple bridge and full scale computer.
- Battery operated–no shock hazards. Rechargeable.
- Will work with any thermistor catheter on the market; including Swan-Ganz balloon flow-directed catheter.
- Equipped with a recorder output.
- Provides information on the area under the dilution curve. (Extrapolates the dilution curve!)
- Price: $1,540.00



THERMO AND DYE DILUTION CARDIAC OUTPUT COMPUTER

- Equipped with Thermodilution and/or Dye Dilution Densitometer
- Easy calibration, automatic zeroing.
- Remote control by foot switch.
- Digital readout in L/min.
- Recorder outputs.

COLUMBUS INSTRUMENTS

Div. of International Instruments Co.

P. O. Box 5244 Columbus, Ohio 43212
Telephone: (614) 488-6176

You expect a lot from a pacemaker with a 36 month full replacement warranty.

And you get a lot from the IDP-54:

An implantable R-wave-inhibited pacemaker for intracardial and myocardial stimulation for a low, constant stimulation threshold.*

Low energy consuming circuitry and the new Mallory cell producing up to 4 to 5 years operating life.

36 month full replacement warranty.

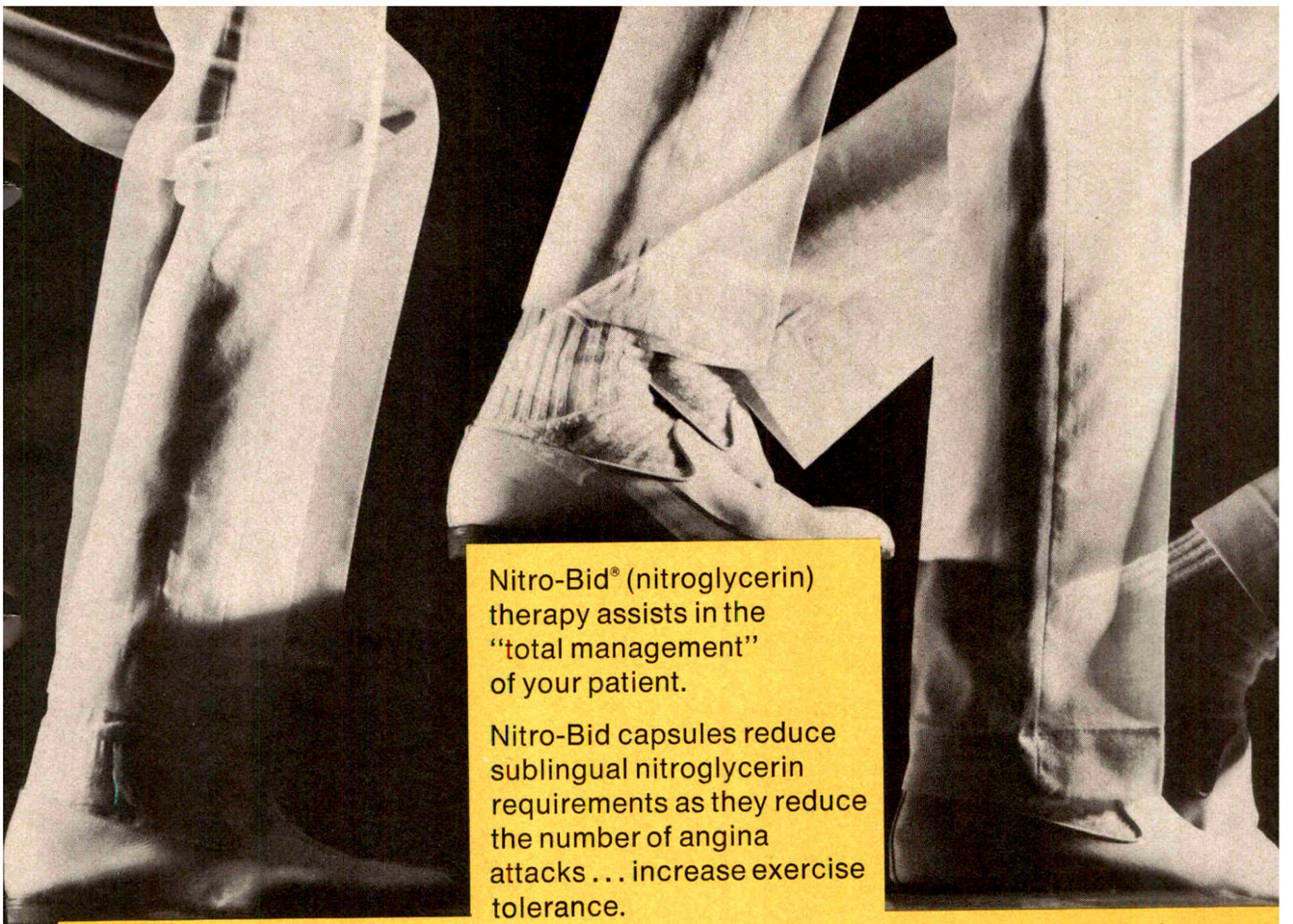
Suitability for initial implant or implantation in patients with existing implanted electrode systems.

* The implantation of an R-wave-inhibited pacemaker has been well proven in the following cases: intermittent AV block with predominant sinus rhythm, recurrent bradycardia and second implantation to replace a fixed rate pacemaker with virtual return to sinus rhythm.

Get to know Biotronik, the pacemakers known for quality.

BIOTRONIK SALES, INC.
9228 4th Street North,
St Petersburg, Florida 33702.
Phone (813) 898-4993

Biotronik Sales, Inc., A subsidiary of Biotronik, Berlin, Germany



Nitro-Bid® (nitroglycerin) therapy assists in the "total management" of your patient.

Nitro-Bid capsules reduce sublingual nitroglycerin requirements as they reduce the number of angina attacks . . . increase exercise tolerance.

The Third Step in Angina.*

After the classic "2-Step" Test aids in a diagnosis of angina, sustained-release Nitro-Bid® (nitroglycerin) is a logical third step. Here's why.

In angina secondary to arteriosclerotic heart disease, sustained-release Nitro-Bid Plateau CAPS® provide a metered sequence of medication during the night to protect against nocturnal angina attack.

In titrating dosage, availability of different strengths "...is quite an asset..."[1]

Nitro-Bid 2.5 and Nitro-Bid 6.5 capsules afford two dosage strengths for convenience in increasing or decreasing dose to accommodate patient symptoms.

NITRO-BID® 2.5
(nitroglycerin 2.5 mg) Plateau CAPS®

NITRO-BID® 6.5
(nitroglycerin 6.5 mg) Plateau CAPS®

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

*"Possibly" effective:
For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12 hour intervals.
Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

Another patient benefit product from PHARMACEUTICAL DIVISION MARION LABORATORIES, INC. KANSAS CITY MISSOURI 64137

Make Life Easier For You And Your Pacer Patients

Now, with the advent of the ESB Medcor Pacer-Check* system, it is possible for your office to conduct regular, accurate recordings of heart pacer patient's ECG and pacer rates by telephone.

Both you and your patients benefit. Now, with no more than a phone call, you can have information which permits elective decisions on replacement rather than emergency or prophylactic replacements. (By using a regular patient checking program, maximum pacer life can be realized.) Your patient and you have flexibility and safety at the same time.

This two-component system operates simply, requiring minimal training to both your personnel and patients.

The Medic Unit, at left, is the central component and is usually located in the hospital or clinic. It receives ECG and pacer rate input via unaltered telephones from the Patient Unit which is usually located in the patient's home. ECG data, produced on a standard paper chart, indicates the relationship between the QRS complex and pacer artifact to ascertain pacer capture. Pacer rate is shown continuously by illuminated numbers on the front panel. This is the first system available to physicians that records ECG and simultaneously displays pacer rate.

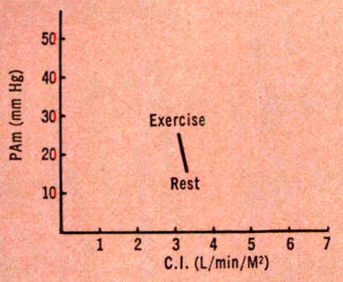
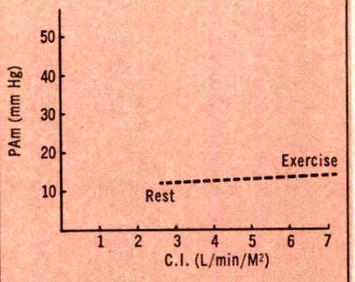
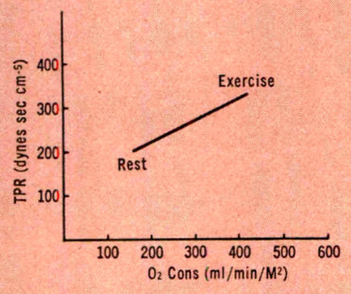
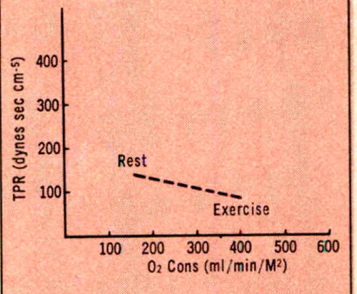
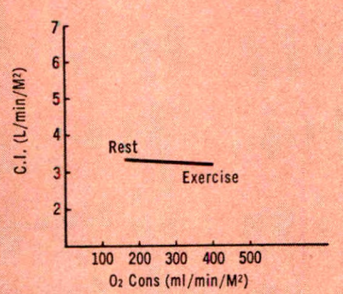
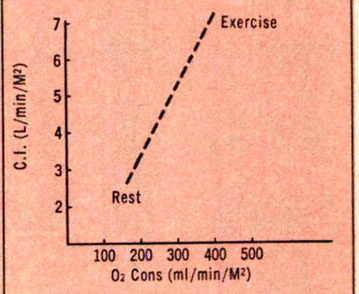
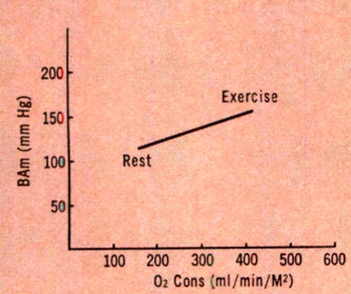
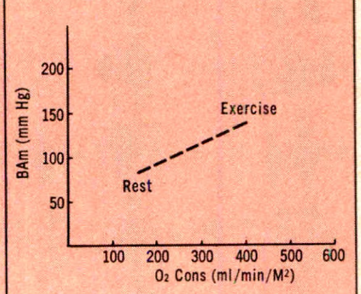
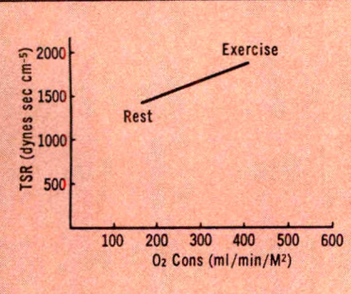
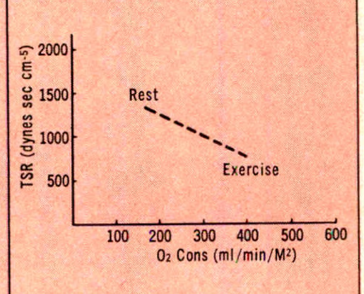
The Patient Unit is lightweight and battery powered. It is capable of transmitting from any telephone to your office. Transmissions have been successfully made from such great distances as Tokyo to New York. To operate, the patient places the telephone headset in the receiving cradle and then slips the two expandable bracelets over his forearms. Transmission begins immediately.

The Pacer-Check* system, approved for reimbursement by Medicare, has proven itself a useful and self-supporting method of maintaining a desirable pacer program.

If the unique qualities of the Pacer-Check* system interest you, contact ESB Medcor, Inc., Dept. 373, 5920 Rodman St., Hollywood, Florida 33023. Toll free call: (800) 327-9780, Ext. 373.

ESB Medcor™

HEMODYNAMICS OF ANGINA PECTORIS* — PATIENTS RESTING AND EXERCISING, BEFORE AND AFTER ISORDIL® SUBLINGUAL
(isosorbide dinitrate)

BEFORE MEDICATION		AFTER 5 mg. ISORDIL SUBLINGUAL (isosorbide dinitrate)
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

IN ANGINA PECTORIS*

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday stress

ISORDIL® SUBLINGUAL
(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

IVES LABORATORIES INC.
New York, N.Y. 10017

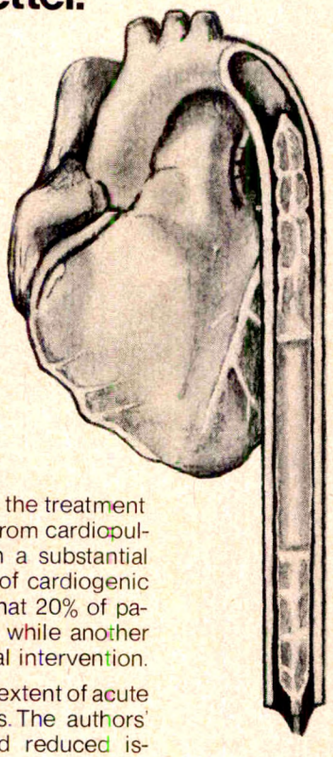
DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.

"a life-saving measure in a substantial minority of patients"[1]

The Avco Intra-Aortic Balloon Pump* ...and the Sooner, the Better.

The rationale of intra-aortic balloon pump (IABP) therapy in low-cardiac output conditions is widely accepted. By lowering pressure in the proximal aorta at the beginning of systole, myocardial work load is lessened. Also, by augmenting pressure during early diastole, pumping improves coronary perfusion and can open dormant collaterals. Thus a better balance between myocardial oxygen demand and consumption is obtained.



Documented effectiveness

The IABP's effectiveness is clinically proven in the treatment of cardiogenic shock and in weaning patients from cardiopulmonary bypass. It is a "lifesaving measure in a substantial minority of patients who would otherwise die of cardiogenic shock."[1] Braunwald and Maroko[2] estimate that 20% of patients who would otherwise die can be saved, while another 20% can be stabilized for diagnosis and surgical intervention.

IABP "significantly reduced the magnitude and extent of acute myocardial ischemic injury"[3] in animal studies. The authors' preliminary clinical results also demonstrated reduced ischemia as well as hemodynamic improvement.

Time a critical factor

Hemodynamic criteria to determine if a patient who seems to be going into cardiogenic shock is responding to treatment have been developed by Leinbach.[4] These criteria are a major contribution to the effective application of IABP treatment since *early use* of the system greatly increases the chances of success. Buckley and associates[5] used the IABP in 27 heart-surgery patients who went into shock upon termination of cardiopulmonary bypass. Eighteen survived; 13 are long term survivors. Best results occurred with initiation of IABP therapy early in the postoperative period.

*Developed by Avco Corporation and manufactured for Roche Medical Electronics Division.

The IABP versus drugs

Dunkman and others[6] have concluded that "catecholamines may actually increase ventricular dysfunction and necrosis" whereas the IABP's enhancement of coronary perfusion and reduction of oxygen-consuming work in the left ventricle can save patients if applied before about 40% of the left ventricle is irretrievably damaged. Moreover, IABP permits safe use of drugs if needed.

AVCO, the most experienced system

The internal counterpulsation system most widely used clinically is the Avco IABP. There are some very practical reasons for this dominance.

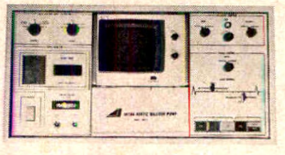
Patented 3-chamber balloon design prevents end occlusion.

QRS triggered synchronization with normal and abnormal rhythms.

Automatic reset for changes in interval or loss of R wave.

Safety engineering with fail-safe venting, self-initiated trouble identification, and emergency compressor with independent power supply.

Nationwide on-site service.



1. Editorial. JAMA 224:245, 1973.
2. Braunwald, E. and Maroko, P.R., Ann. Int. Med. 76:659, 1972.
3. Maroko, P.R. et al. Circulation 45:1150, 1972.
4. Leinbach, R.C., quoted in Emerg. Med. 5:107, 1973.
5. Buckley, M.J. et al (abstract). Circulation 46, Suppl. 2:76, 1972.
6. Dunkman, W.B. et al. Circulation 46:465, 1972.

ROCHE

Write for information on clinical experience and the annual Avco Pump Users' Meeting. Your local representative can arrange an Avco IABP demonstration in either a clinical or experimental setting.

ROCHE MEDICAL ELECTRONICS DIVISION, HOFFMANN - LA ROCHE INC., CRANBURY, N.J. 08512

See us at the American Association for Thoracic Surgery Convention Booth #703

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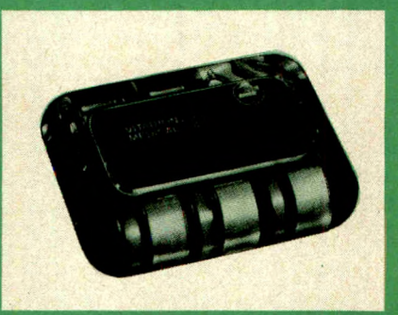
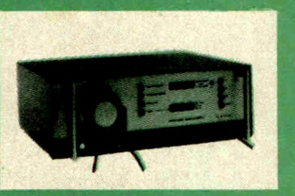




Vitatron Medical upgrade pacemaker reliability

Vitatron Medical now have upgraded the reliability of their pacemakers by application of a new HgO-Zn battery. This battery was specially designed for pacemakers and has a higher energy density and a better dependability.

Battery failure rate is no more than 0.05%/1000h. This new development, together with the battery switch reduces current consumption during transportation and storage to an absolute minimum, increasing pacemaker longevity by 50%.

The small dimensions, light weight, ideal shape and easy electrode connection make the new generation of Vitatron Medical pacemakers extremely easy to implant and assure a minimum of post-operative complications.

The unique intracardial electrode type MIP 2000 with means for fixation to the heartwall allows accurate placement of transvenous electrodes in more difficult cases.

Pacemaker follow-up reliability is achieved by Vitatron Medical's completely analysable pacing system consisting of the VCA pacemaker and the fully automized type MPA 1 digital pacemaker analyzer.

VITATRON MEDICAL

For detailed technical information write:
VITATRON MEDICAL B.V., P.O. Box 76, NL 6210 Dieren, Holland
VITATRON MEDICAL INC., 464 Granite Ave , Milton, Mass. 02186 (USA)

bureau IPS rotterdam

NEW FROM AYERST

the "healthy" hypertensive

It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

DIUCARDIN provides approximately the same diuretic potency as hydrochlorothiazide at maximal therapeutic dosage. With DIUCARDIN, the onset of diuresis is gradual and may be maintained for twelve hours or more with a single dose.[1,2] The antihypertensive effect of DIUCARDIN is usually maintained in long term use. For many patients on DIUCARDIN, a convenient once-a-day dosage may suffice.

Based on efficacy *and* economy, DIUCARDIN provides a good beginning for many hypertensive patients. New DIUCARDIN 50 mg. Tablets. For mild to moderate hypertension and adjunctive therapy for many types of edema.

Ayerst®

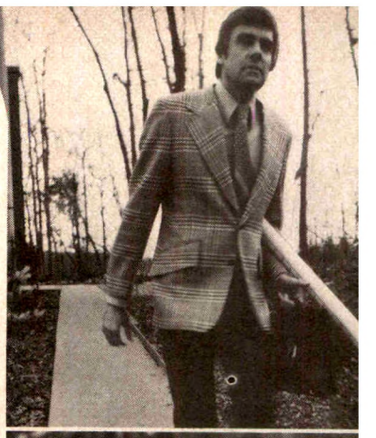
controlled early on

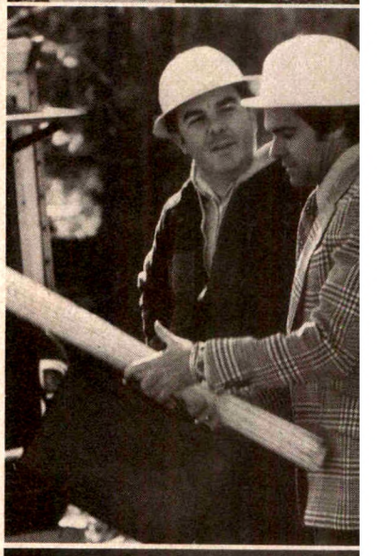
Diucardin® TABLETS

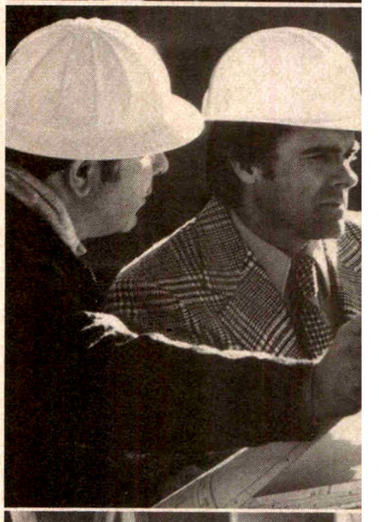
(hydroflumethiazide)

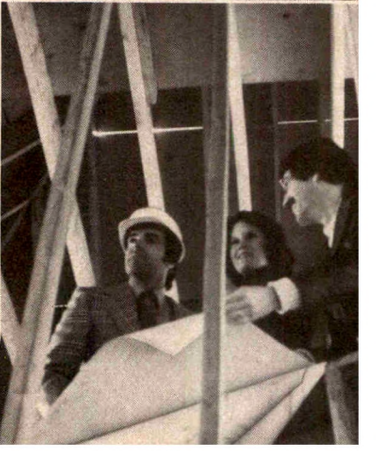
diuretic/antihypertensive

(See prescribing information on next page.)









NEW FROM AYERST

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

diuretic/antihypertensive

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: **Hypertension:** DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN — No. 702 — Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

makers of
Inderal® (propranolol hydrochloride),
Atromid-S® (clofibrate),
& Premarin® (Conjugated Estrogens Tablets, U.S.P.)

7413

Bright new talk show.

We've just come out with a series of patient monitoring modules that are completely new. From their brighter digital displays to their broader capabilities, they talk to you loud and clear.

First the digital displays.

Characters are more than a ½ inch high, and they form solid lines of light which are easily readable across a room or down a corridor.

They flash HI, LO and OFF (in response to high and low alarms and leads off) and, of course, numerical values.

All alarm set points can be read directly on the digital display, improving the accuracy of the setting.

Displays can be darkened at night so as not to disturb a patient. In the event of an alarm, they automatically re-appear.

Now for capability.

Our HR-3 Digital Heart Rate Module is physically independent of the ECG amplifier and can be placed at bedside, central station, or both. It monitors heart rate and eliminates artifacts. It even ignores pacemaker spikes when used with B-D Electrodyne's new ECG amplifier.

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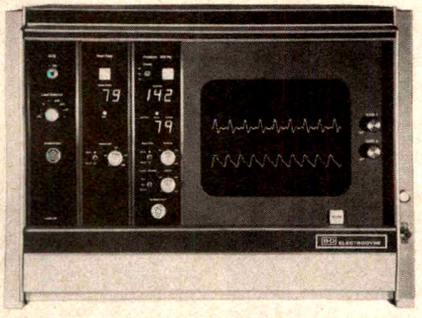

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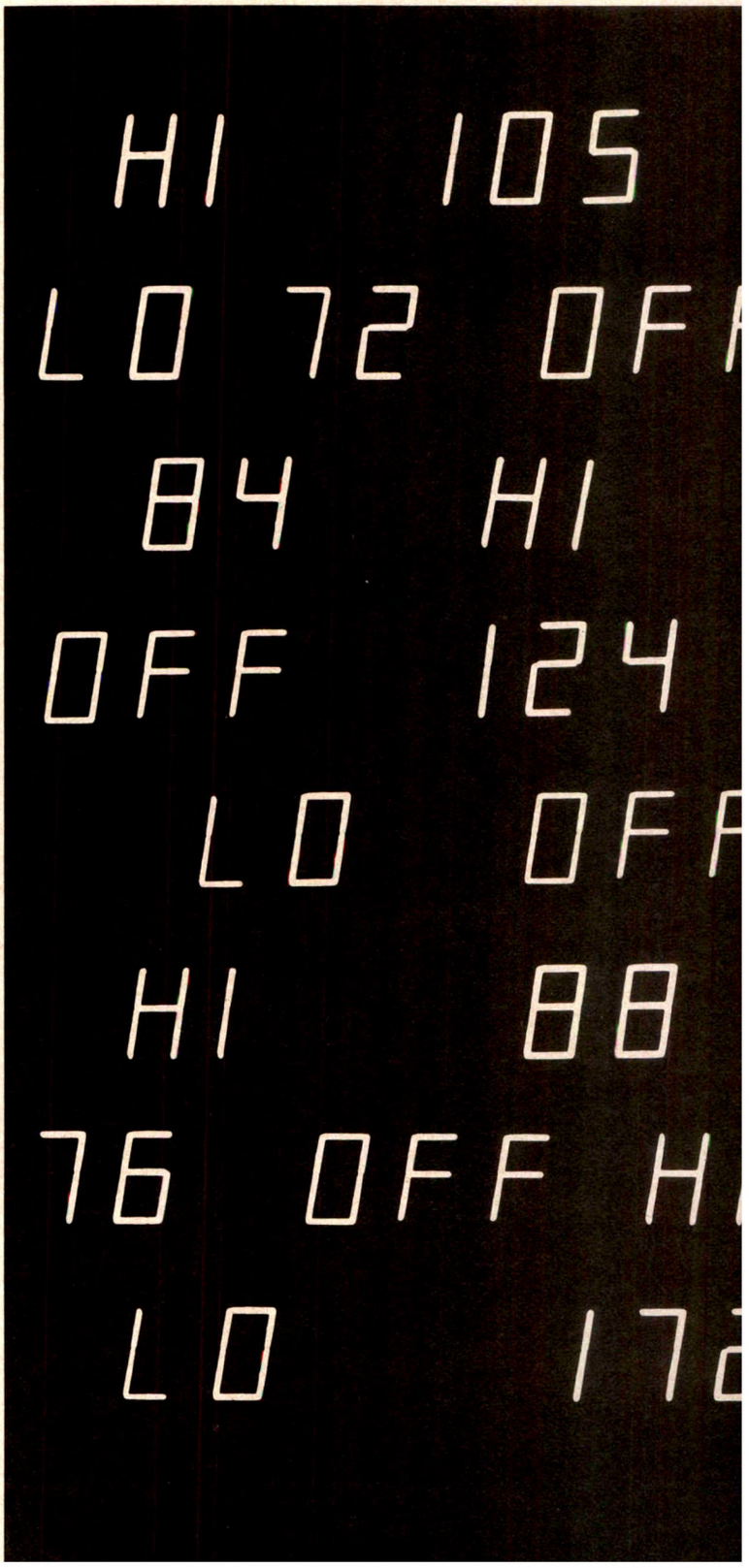

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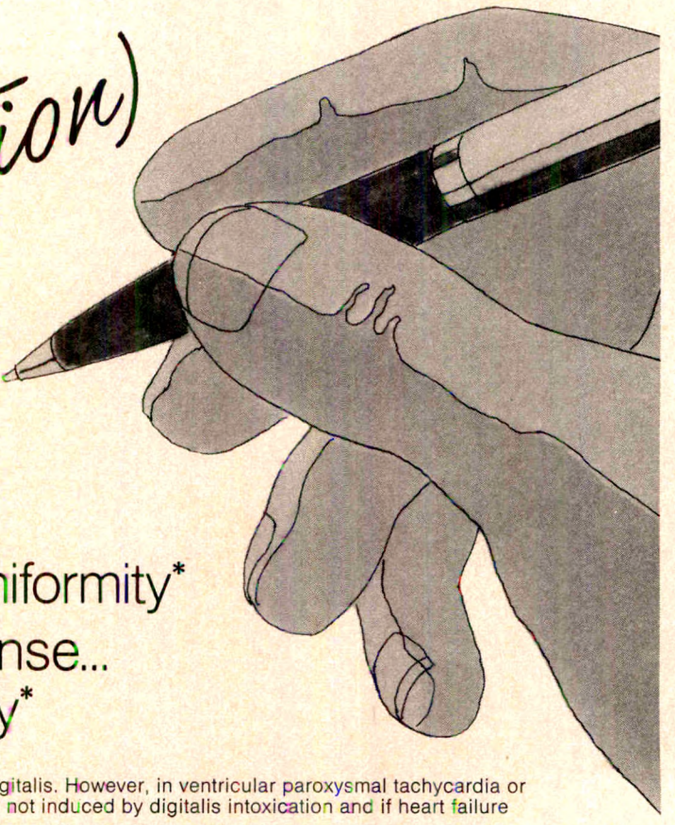

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The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 3

CLINICAL STUDIES

Atropine-Induced Cardioacceleration and Myocardial Blood Flow in Subjects With and Without Coronary Artery Disease

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Thirty-five patients being studied by coronary cineangiography for diagnosis or evaluation of coronary atherosclerotic occlusive disease had myocardial blood flow determinations at rest and after intravenous administration of atropine sulfate, 1.0 mg. Myocardial blood flow was determined by a coincidence counting system and a single bolus injection of ^{84}rubidium chloride.

In 10 patients without coronary occlusive disease, heart rate increased by 52 percent and myocardial blood flow by 48 percent ($P < 0.001$, $r = 0.888$). In 14 patients with single vessel disease or partial occlusion of two vessels, myocardial blood flow increased by 44 percent and heart rate by 37 percent ($P < 0.05$, $r = 0.553$). In 11 patients with two or three vessel occlusive disease, heart rate increased by 30 percent whereas myocardial blood flow increased by only 15 percent ($r = -0.172$).

We conclude that patients with two and three vessel involvement by atherosclerotic occlusive disease are unable to increase nutrient myocardial blood flow in response to atropine-induced cardioacceleration to the same degree as patients without coronary disease or with less extensive disease. The observation may be of therapeutic importance because of the potential that administration of atropine may have for inducing myocardial ischemia in such patients.

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Atropine has been considered useful in the management of bradycardia and ventricular ectopic activity in acute myocardial ischemia[1] and in the prehospitalization phase of coronary insufficiency as a possible antiarrhythmic agent.[2] However, atropine may produce deleterious effects in the presence of myocardial infarction by increasing the degree of myocardial ischemia probably by way of an increase in myocardial oxygen need secondary to increased heart rate.[3,4] And, serious ventricular arrhythmias appearing after the administration of atropine to patients with acute myocardial infarction have been reported,[4–6] perhaps reflecting increasing ischemia.

Clinically, the adverse effects of atropine-induced tachycardia on exercise tolerance in patients with coronary artery disease have been recognized for many years.[7] However, little information is available on the effects of atropine itself on myocardial blood flow. The drug has been primarily used in animal studies as a parasympatholytic agent and as an adjunctive agent in pacing studies in man.

This study compares the effect of atropine-induced cardioacceleration on nutrient myocardial blood flow, as measured by a coincidence counting system and single bolus injection of ^{84}rubidium chloride in patients with and without coronary occlusive disease of various degrees of severity.

Methods

Thirty-five consecutive patients undergoing selective coronary cinearteriographic studies for diagnosis or evaluation of coronary arteriosclerotic occlusive disease had myocardial blood flow determinations at rest and 3 minutes after intravenous administration of 1.0 mg of atropine sulfate. All studies were performed just before the arteriographic study, in the morning, with the patients in a fasting state, without sedation, and in the supine position.

A catheter was passed through the basilic vein and positioned in the high right atrium. A short polyethylene catheter (approximately 18 gauge) was introduced percutaneously into the right femoral artery. Blood pressure, measured by means of the indwelling catheter in the femoral artery connected to a Statham P23D strain gauge transducer, was recorded on a Sanborn recorder (model 150). The mean arterial pressure was obtained by electrical integration and the mean systolic arterial pressure by planimetric integration. Pressure-time per minute expressed in millimeters of mercury per second per minute was obtained as the product of systolic mean arterial pressure, heart rate and systolic ejection period. Systolic ejection period in seconds was measured from the pressure records as the time interval between the onset of the femoral arterial pulse and the dicrotic notch and was expressed as the average figure of at least six beats taken at the extremes of respiratory fluctuation. Heart rate was measured from a simultaneously recorded electrocardiogram. The cardiac output was determined using ^{84}rubidium chloride as the indicator.[8]

Myocardial blood flow (MBF) in milliliters per minute per total heart was calculated using the formula:

$$MBF = q(t)/\int_0^\infty A_0(t)dt$$

where q(t) is the myocardial uptake of ^{84}rubidium chloride as measured by the coincidence counting system and $\int_0^\infty A_0(t)dt$ represents the concentration of the isotope in arterial blood during the first circulation, determined by extrapolation after recirculation begins. The theoretical basis of this formulation and experimental verification have been reported in detail.[8–12]

Control measurements were made during sinus rhythm. Then 1.0 mg of atropine sulfate was administered intravenously and repeat measurements were made 3 minutes later. If angina pectoris occurred, the measurements were repeated during the anginal episode.

Coronary cineangiography was performed after completion of the myocardial blood flow and hemodynamic determinations. Multiple oblique views were obtained using renographic contrast medium. Injections were made before and after sublingual administration of nitrites. Recording was performed with 35 mm Kodak Double-X film developed in Ethol-90. A Phillips 6-inch image intensifier was utilized with a 100 mm lens at 64 frames/sec. Only patients with cineangiograms of good quality in multiple projections of all three major coronary vessels were included in this study.

Classification of the coronary arterial lesions was performed as follows: Each of the three major coronary vessels (right, left anterior descending and circumflex) was given a rating of 100; a value of 200 was assigned to the left main coronary artery. The number of vessels involved was then determined (from one to three) and the percent of vessel remaining patent was estimated in increments of 25 percent. In the case of branch stenosis, the degree of occlusion was estimated according to the technique of Rowe et al.[13] For example, if the left anterior descending coronary artery bifurcated, giving off a branch about 50 percent of the size of the parent artery, and if this branch were 50 percent occluded, the estimated occlusion of the branch vessel would be equivalent to 25 percent occlusion of the left anterior descending coronary artery. A final index was then based on the estimated percent of lumen of all three vessels remaining open (a value of 300 equaling no occlusive disease). The cinearteriograms were interpreted independently by three investigators without availability of the physiologic data. Data were analyzed as the significance of the difference between the means of paired data.

Results

Patients without coronary artery disease: In the 10 patients without coronary artery disease, intravenous administration of 1.0 mg of atropine sulfate resulted in a 52 percent increase in heart rate ($P < 0.001$) and a 48 percent increase in myocardial blood flow ($P < 0.001$) (Table IA). There was a significant correlation ($P < 0.001$) between the change in heart rate and myocardial blood flow ($r = 0.888$). Significant changes also occurred in pressure-time per minute ($P < 0.001$), cardiac output ($P < 0.01$) and diastolic pressure ($P < 0.01$). The arterial mean blood pressure increased insignificantly. None of these patients had systemic hypertension or clinically detectable heart disease of any type.

Patients with coronary occlusive disease: In the 25 patients with various degrees of coronary occlusion, heart rate increased by 34 percent ($P < 0.001$) and myocardial blood flow by 31 percent. The relation between the change in heart rate and myocardial blood flow had a correlation coefficient of $r = 0.496$ ($P < 0.025$). Cardiac output increased significantly ($P < 0.001$) as did pressure-time per minute and arterial mean and diastolic pressures ($P < 0.001$).

The patients with coronary artery disease were then classified in two groups, Group 1 comprising 14 patients with a coronary artery index of 150 or greater, and Group 2, 11 patients with a coronary artery index of less than 150. This classification was undertaken to determine the effect of increasing severity of obstructive disease on myocardial blood flow reserve in response to atropine.

Patients in Group 1 manifested a 37 percent increase in heart rate and a 44 percent increase in myocardial blood flow; both changes were significant (P

TABLE I

Myocardial Blood Flow and Hemodynamic Changes with Atropine

Case no.	Age (yr) & Sex	CAI	Heart Rate		MBF		CO		PTM		Arterial Mean		Diastolic	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
A. Patients Without Coronary Artery Disease														
1	44M	300	68	82	185	222	3.5	3.3	2337	2583	96	98	75	78
2	47M	300	68	84	170	208	4.1	4.7	2337	2681	100	100	65	70
3	32M	300	92	150	263	446	4.6	6.0	2701	3480	92	99	74	84
4	42M	300	80	94	190	211	3.8	4.3	2472	2402	76	73	58	59
5	46M	300	74	142	107	210	3.1	4.0	2691	3720	98	107	76	90
6	43M	300	80	133	213	293	4.2	6.0	2309	2581	95	95	70	70
7	36M	300	78	142	212	316	5.8	5.6	2756	3496	110	105	85	87
8	36M	300	82	108	201	269	4.3	4.3	2493	2755	115	113	85	88
9	56M	300	60	104	175	291	3.7	4.1	2344	3483	93	100	60	72
10	45M	300	84	130	235	386	5.0	5.5	2589	2866	92	98	57	61
Average	42.7		76.6	116.9	195.1	285.2	4.2	4.8	2502.9	3004.7	96.7	98.8	70.5	75.9
SD	±8.4		±9.3	±25.5	±41.8	±80.5	±0.8	±0.9	±171.6	±484.7	±10.6	±10.5	±10.3	±11.2
P			<0.001		<0.001		<0.01		<0.001		NS		<0.01	
B. Group 1. Patients With a Coronary Artery Index of >150														
11	56M	200	66	94	90	120	2.8	3.8	1943	2363	78	90	60	75
12	62M	200	72	96	156	215	4.5	5.7	3094	3744	99	101	70	76
13	47M	175	76	108	220	335	4.8	4.9	2918	3260	91	95	70	75
14	54M	250	72	120	162	215	4.1	4.3	2921	3032	100	108	70	80
15	51M	175	74	106	162	264	5.8	6.9	2029	2565	77	85	62	73
16	50M	200	84	102	178	267	3.6	4.0	2373	2891	86	91	64	70
17	42M	200	84	114	205	213	4.3	4.5	2220	2677	95	95	72	72
18	46M	200	82	112	109	159	3.5	4.0	2882	3768	90	105	73	90
19	56F	200	66	88	131	153	2.7	3.3	2642	2825	87	94	68	72
20	46M	200	66	90	126	183	3.4	4.4	1749	1908	90	87	65	70
21	59F	225	86	110	138	145	2.5	2.7	1535	1883	73	82	55	65
22	51M	200	82	112	153	354	5.2	6.3	2513	2703	92	93	74	75
23	36M	150	86	112	136	278	4.0	4.1	2122	1754	83	85	65	65
24	52M	150	80	80	134	132	2.9	3.1	1742	1725	75	82	65	65
Average	50.5		76.8	103.1	150.0	216.6	3.9	4.4	2334.5	2649.9	86.9	92.4	66.6	73.1
SD	±6.8		±7.5	±11.7	±34.9	±74.2	±0.9	±1.2	±505.9	±676.2	±8.7	±8.1	±5.4	±6.6
P			<0.001		<0.001		<0.001		<0.002		<0.001		<0.001	
C. Group 2. Patients With a Coronary Artery Index of <150														
25	30M	125	94	116	182	271	4.8	5.3	1880	2285	93	97	68	78
26	53M	125	52	73	192	213	3.1	4.1	1926	2489	88	95	63	70
27	46F	125	86	120	230	191	4.4	4.4	1891	2576	97	109	70	75
28	30M	125	84	110	156	186	3.7	4.9	2420	3274	88	102	76	86
29	45M	50	55	72	123	124*	3.9	5.6	1401	1882	76	81	55	60
30	38M	100	64	81	177	202	3.1	4.0	1933	1940	85	90	65	65
31	45M	50	56	68	161	151	4.7	4.3	1377	1773	70	75	45	55
32	47M	50	82	106	99	163	2.6	4.2	2285	2774	81	88	63	67
33	49M	125	62	80	185	219	3.1	3.3	1953	2552	73	85	55	65
34	48M	50	86	116	100	126	4.9	5.6	2195	2299	83	78	63	78
35	56M	125	78	90	231	281	4.8	4.5	2300	2192	90	93	60	65
Average	47.8		72.6	93.8	166.9	193.4	3.9	4.6	2169.8	2366.9	84.0	90.3	62.1	69.2
SD	±8.1		±15.0	±20.1	±45.3	±51.9	±0.9	±0.7	±339.6	±435.1	±8.4	±10.3	±8.4	±8.8
P			<0.001		<0.025		<0.01		<0.005		<0.002		<0.001	

*Angina.

Arterial mean = arterial mean pressure (mm Hg); CAI = coronary artery index (see text for derivation); CO = cardiac output (liters min); diastolic = mean arterial diastolic pressure (mm Hg); MBF = myocardial blood flow (ml/min per total heart); NS = not signif cant; *P* indicates probability value for change after administration of atropine. PTM = pressure-time (mm Hg/sec per min); SD = standard deviation.

<0.001). The correlation between the change in heart rate and myocardial blood flow was significant at the $P < 0.05$ ($r = 0.553$) level. As in the entire group of patients with coronary occlusive disease, cardiac output, arterial mean and diastolic pressures increased significantly ($P < 0.001$) as well as pressure-time per minute ($P < 0.002$).

In patients in Group 2 (Table IC), those with two and three vessel coronary disease, heart rate increased by 30 percent ($P < 0.001$) and myocardial blood flow by 15 percent ($P < 0.025$). There was a negative correlation ($r = -0.172$) between these two variables. Cardiac output, pressure work, arterial mean and diastolic pressures all increased significantly ($P < 0.001$).

Discussion

Very few clinical studies were available with which to compare our data on the hemodynamic effects of atropine-induced changes in heart rate. Gorlin et al.[14] reported a linear increase in heart rate and coronary blood flow, as measured by the nitrous oxide technique, in six patients, three with valvular heart disease. In their study, a 38 percent increase in heart rate resulted in a 38 percent increase in coronary blood flow and a 33 percent increase in myocardial oxygen consumption. The cardiac output data from their study and those reported here are probably not comparable because of differences in patient group, the unknown sedation factor, calculation in cardiac index versus cardiac output, and so forth. The increase in mean arterial and diastolic pressures was not significant in the study of Gorlin et al., whereas it was in our study. This discrepancy may also be due to differences in number and type of patients, the sedation factor or other differences between the experimental situation in the two studies. McMichael and Sharpey-Schafer[15] reported an increase in cardiac output in 8 of 10 subjects given 1 mg of atropine intravenously. Changes in systemic blood pressure were not reported.

As quoted by Ross,[7] Wayne and LaPlace concluded from exercise stress testing concomitant with administration of atropine that, "the diminution in the number of efforts (trips up the steps) and the increase in the duration of pain under atropine . . . can be attributed . . . to the more rapid action of the heart, which increases its energy expenditure without a concomitant increase in coronary flow . . . ." The data presented here which demonstrate a decreased rate of increase in myocardial blood flow with atropine in patients with two and three vessel coronary artery disease, as a group, as compared with patients with single vessel disease or no occlusive disease are in accord with the above clinical observation. To make that conclusion it must be assumed, however, that linearity between heart rate and flow normally maintains for each increment in rate,[16] all other factors controlling myocardial oxygen consumption remaining equal.

Comparison of normal patients and those with two or three vessel disease: If one assumes that the normal subjects and those with a coronary artery index of less than 150 (Group 2) had had the same increase in heart rate (52 percent), simple linearity comparisons would show that patients in Group 2 would have had a 26 percent increase in blood flow rather than the 48 percent increase demonstrated by the normal subjects. Conversely, if the normal subjects had had an increase in heart rate of only 30 percent, as did patients in Group 2, blood flow in the normal group would have increased by only 28 percent. The difference between the 15 percent increase in blood flow manifested by patients in Group 2 and the 28 percent projected increase in the normal subjects at the same heart rate is significant ($P < 0.02$) from binomial calculation. However, if at a smaller increase in heart rate, myocardial oxygen demand did not increase proportionally, then the response of our patients with two and three vessel disease may not be abnormal since heart rate in this group increased less than in patients without coronary disease.

The problem as it relates to myocardial oxygen consumption and heart rate cannot be answered here since myocardial oxygen consumption was not measured in our patients. Such measurements require a steady state as well as coronary sinus catheterization, and neither condition was included in our experimental design. In addition, there is controversy concerning the accuracy of coronary sinus oxygen determinations in the presence of the heterogeneity of blood flow that occurs in coronary artery disease. Linearity between incremental cardioacceleration produced by right atrial pacing and coronary sinus blood flow values has been demonstrated and shown to exist in patients with coronary disease,[17] but atropine and right atrial pacing may be different interventions. That they are indeed different may be inferred from the fact that, with atropine, the increase in pressure-time per minute did not correlate with the increase in myocardial blood flow in our normal patients to the same degree that occurs with right atrial pacing.[18] With right atrial pacing, the correlation between heart rate and myocardial blood flow increase is highly significant.[18] Perhaps atropine alters another determinant of myocardial oxygen consumption, such as ventricular volume or atrial or ventricular contractility,[19–22] or perhaps a disproportionate increase in flow reflects a direct effect of the drug on coronary vascular resistance.[23–25] In addition, the level of mean arterial pressure in our patients with coronary disease was not as high as in the normal patients. This reduced arterial pressure influences pressure work and may alter blood flow characteristics.

We are not able to explain why patients with coronary artery disease had a smaller increase in heart rate at identical doses of atropine than normal patients. The ages of the patients were comparable, and medications such as digitalis or propranolol were not being taken by either group during or shortly before the study. One recent experimental study[26] showed a

relation between ischemia in the sinus node and sinus rate. Another explanation might be that the patients with coronary disease had less vagal tone, perhaps for psychological reasons, than the patients without disease. The depressed rate response in the patients with coronary disease may have been "protective" in a sense since only one patient experienced angina during the procedure. Clinically, however, we have observed the development of angina after prophylactic administration of atropine before coronary cineangiography.

Limitations of method: Validation of the coincidence counting technique for quantitatively measuring myocardial blood flow in man has been and continues to be a difficult problem. The assumption that the myocardial extraction ratio for rubidium is the same as the extraction ratio for the total body, upon which the application of Sapirstein's formulation[27] rests, has been tested to only a limited degree.[12,28] And even if concomitant myocardial and total body extraction ratios could be accurately measured with every intervention, it is not clear that the problem would be solved. With the known heterogeneity of blood flow in coronary artery disease,[29,30] the extraction ratio for the heart in any particular patient undoubtedly represents a composite of extraction ratios.[29] Thus, a change in overall extraction ratio could theoretically occur because of a redistribution of flow and might not necessarily reflect a change in total myocardial nutrient blood flow. For these reasons, plus the problem of nonlinear isotope exchange at various flow rates,[31] we do not claim quantitation for the technique. The data have been analyzed as the difference in group response, abnormal versus normal. It might be preferable to consider the measurement as a "coronary flow equivalent," a term introduced by Bing and associates[32] in relation to the coincidence counting technique.

Clinical implications: With these limitations in mind, we believe our data suggest that atropine-induced cardioacceleration could potentially result in an increased myocardial oxygen demand in excess of the ability to increase nutrient myocardial blood flow in patients with coronary artery occlusive disease. This consideration may be important in balancing the possible benefits of cardioacceleration with atropine against the potential of the drug for increasing myocardial ischemia. It must be noted, however, that our patients had a relatively normal heart rate at rest, and no conclusions can be drawn concerning atropine-induced cardioacceleration from bradycardia to normal heart rate ranges.

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Electrophysiologic Effects of Atropine on Atrioventricular Conduction Studied by His Bundle Electrogram

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The electrophysiologic effects of atropine were studied with His bundle recordings in 14 patients. Administration of atropine, 0.5 mg intravenously, produced a moderate degree of sinus acceleration in all patients (average increase 20 percent over control rate). Atrioventricular (A–V) nodal conduction was enhanced during both sinus rhythm and at various paced atrial rates after administration of atropine. The paced atrial rates at which the A–V nodal Wenckebach phenomenon occurred were significantly higher after administration of the drug than before. Similar effects on retrograde conduction were observed during ventricular pacing. Atropine shortened both the functional and effective refractory periods of the A–V node but appeared to have no direct effect on either His-Purkinje conduction time or refractoriness. However, aberrant ventricular conduction and block within the His-Purkinje system increased during premature atrial stimulation after atropine administration. This was the result of shortening of the functional refractory period of the A–V node by atropine, which produced significantly shorter H_1–H_2 intervals. The effect of atropine on the electrophysiologic properties of the A–V conducting system was important in interpreting the conversion of a type I gap in A–V conduction to a type II gap.

Atropine sulfate, commonly considered a safe drug, is frequently used in general medical practice. Its effects on the electrophysiologic properties of the sinus[1–5] and atrioventricular (A–V) nodes[1,2,6] have been extensively studied. Most clinical studies have used standard electrocardiographic recordings to assess the effects of atropine on total A–V conduction. Relatively few have considered the possible effects of atropine on the His-Purkinje system.

In this investigation we used His bundle electrograms to study the effects of atropine on the electrophysiologic properties of the A–V node and His-Purkinje system in 14 patients. A–V nodal and His-Purkinje conduction times were compared at various paced atrial rates before and after administration of the drug. The functional and effective refractory periods of the A–V node and His-Purkinje system were also studied with use of the atrial extrastimulus method.[7,8]

Materials and Methods

All 14 patients were studied in the nonsedated, postabsorptive state after informed consent had been obtained. Under local anesthesia a quadripolar catheter was introduced percutaneously into an antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium. The distal two electrodes were used to pace the atrium, and the proximal electrodes to record high right atrial activity. A tripolar electrode catheter was percutaneously introduced into the femoral vein and positioned in the tricuspid

From the Cardiopulmonary Laboratory, U. S. Public Health Service Hospital, Staten Island, N. Y. This work was supported in part by the Federal Health Program Service, U.S. Public Health Service Project Py 73-1 and National Heart and Lung Institute Project HE 12536-04. Manuscript accepted June 20, 1973.

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TABLE I

Effect of Atropine on Sinus Cycle Length and Antegrade Conduction (msec)

Case no.	Age (yr)	Diagnosis	Atropine	Sinus Cycle Length	A–H	H–V
1	57	NHD	Before	950	105	50
			After	840	80	50
2	54	IHD	Before	1200	100	62
			After	870	80	62
3	57	NHD	Before	1100	80	45
			After	950	65	45
4	69	IHD	Before	810	85	45
			After	740	75	45
5	68	NHD	Before	860	75	40
			After	670	60	40
6	53	IHD	Before	750	90	45
			After	640	60	45
7	63	NHD	Before	860	85	50
			After	750	80	50
8	36	NHD	Before	720	90	40
			After	600	70	40
9	34	NHD	Before	800	65	50
			After	720	60	50
10	68	IHD	Before	860	100	35
			After	770	90	35
11	53	IHD	Before	740	80	60
			After	610	60	60
12	52	NHD	Before	750	90	50
			After	680	85	50
13	19	NHD	Before	680	80	45
			After	550	70	45
14	75	NHD	Before	690	100	40
			After	660	85	40

IHD = ischemic heart disease; NHD = no heart disease.

valve area to record electrical activity of the His bundle as previously described.[9] For ventricular pacing a bipolar catheter was inserted into another arm vein and positioned at the apex of the right ventricle.

Atrial pacing was accomplished by using a programmed digital stimulator that delivered rectangular impulses of 1.5 msec duration at approximately twice diastolic threshold. Ventricular pacing was accomplished in a similar way using the lowest milliamperage that permitted reliable capture. Refractory period studies were performed with the atrial extrastimulus method.[7,8]

Three to four standard electrocardiographic leads (I, II, III, V_1) were simultaneously recorded.

All tracings were displayed on a multichannel oscilloscope and recorded on magnetic tape. The recordings were subsequently reproduced at a paper speed of 150 mm/sec. Intracardiac electrograms were recorded at a filter frequency setting of 40 to 500 Hz. Care was taken to insure the grounding of all equipment.

After control values were obtained, 0.5 mg of atropine sulfate was administered intravenously and studies were repeated 5 to 10 minutes after injection. The A–H interval, used as an approximation of A–V nodal conduction time, was measured from the onset of the low right atrial electrogram to the beginning of the His deflection (normal values for our laboratory 60 to 140 msec). The H–V interval represented His-Purkinje conduction time and was measured from the onset of the His bundle deflection to the beginning of ventricular depolarization (normal values for our laboratory 30 to 55 msec). During ventricular pacing with retrograde conduction the interval from the stimulus artifact to the beginning of the low right atrial electrogram was taken as a measure of ventriculoatrial conduction time.

Definitions for relative, functional and effective refractory periods of the various components of the A–V conduction system have been previously published.[10]

Results

Table I provides the essential clinical data on the 14 patients in this study. All patients had sinus rhythm and normal P–R intervals; none was taking medication. Patients with the so-called sick sinus syndrome were excluded from the study.

Sinus cycle: Administration of atropine, 0.5 mg, resulted in an acceleration of the sinus rate in all patients (Table I). The average increase was 15 beats/min (a 20 percent decrease in sinus cycle length).

A–V Conduction Studies

Antegrade conduction: Administration of atropine resulted in significant enhancement of A–V nodal conduction in all 13 patients studied,* as shown by shortening of the A–H interval during sinus rhythm (Table I) and at various paced atrial rates. For example, at a paced atrial rate of 100 beats/min the mean A–H interval measured 113.3 msec (standard error of the mean 9.9 msec) during the control period and 80.0 ± 4.2 msec after administration of atropine ($P < 0.001$). Similarly, in six patients with a paced atrial rate of 150/min the mean decrease in the A–H interval was 33 ± 16 msec after administration of atropine ($P < 0.005$). In seven patients faster rates of atrial stimulation resulted in A–V nodal conduction of the Wenckebach type during the control period. The average atrial rate at the onset of the antegrade A–V nodal Wenckebach phenomenon was 133 beats/min before administration of atropine. After atropine, five of the seven patients demonstrated 1:1 A–V conduction up to an atrial rate of 160 beats/min. Two patients who had an earlier onset of the A–V nodal Wenckebach phenomenon (at atrial rates of 110 and 120 beats/min, respectively) during the control period also demonstrated the phenomenon after atropine administration, but at a much faster atrial rate (150 beats/min in each case). Atropine produced no changes in the H–V interval during antegrade conduction studies.

Retrograde conduction: Retrograde conduction studies were performed in three patients (Cases 6, 11 and 13). At any given paced ventricular rate, retrograde conduction time was less after administration of atropine. The ventricular rate at which the retro-

* Individual patient data on atrioventricular conduction and refractory periods before and after administration of atropine are available on request.

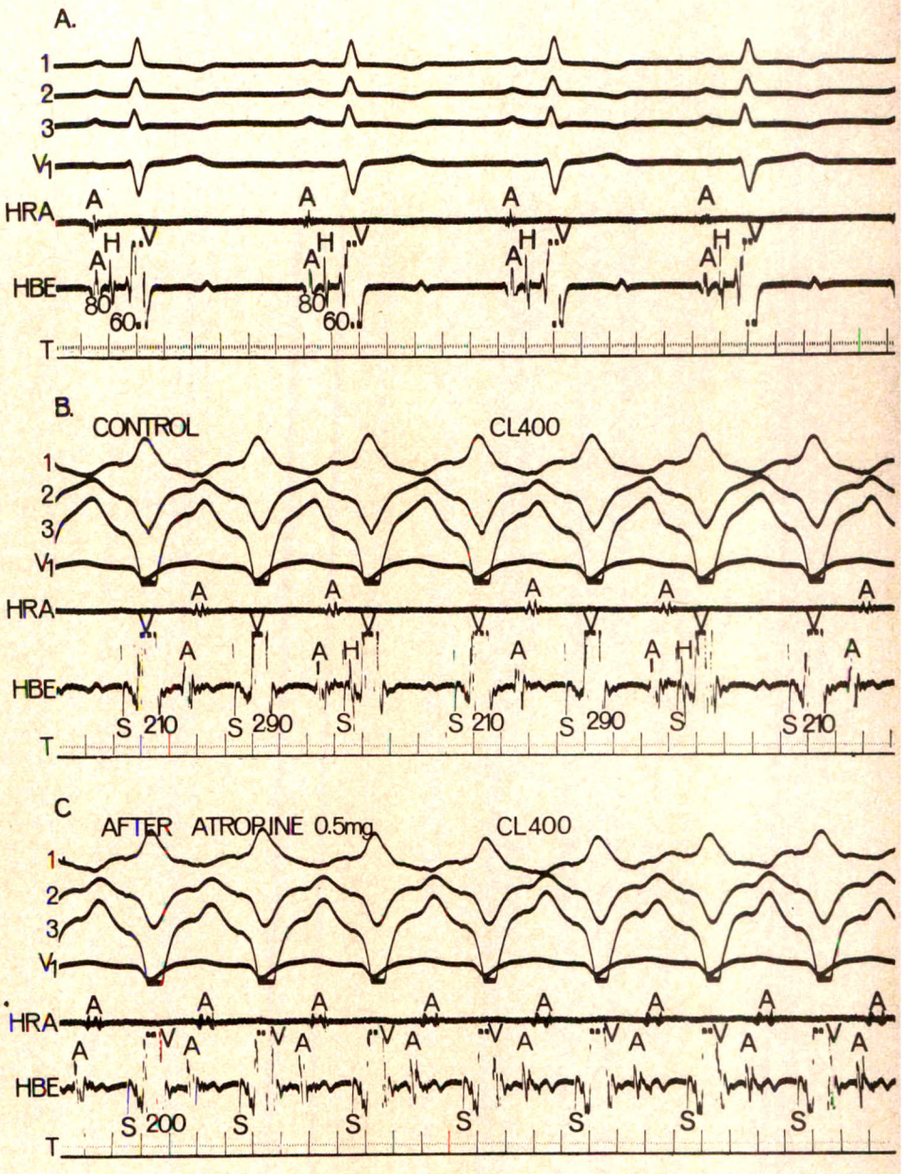

FIGURE 1. Case 11. Effect of atropine on retrograde conduction. **Panel A** shows sinus rhythm in which the sequence of atrial activation is from the high to the low right atrium. **Panel B** demonstrates that at a paced ventricular cycle length of 400 msec a 3:2 retrograde A–V nodal Wenckebach type of block with concealed reentry occurs repetitively. Note the low to high sequence of right atrial activation. **Panel C** shows that after administration of atropine 1:1 retrograde conduction occurs at the same paced cycle length of 400 msec. Each panel shows from top to bottom standard electrocardiographic leads I, II, III, V_1, high right atrial electrogram (HRA), His bundle electrogram (HBE) and time lines (T) recorded at 10 and 100 msec. CL = cycle length; S = stimulus artifact.

grade Wenckebach phenomenon occurred after atropine was greater than in the control period (Fig. 1).

Refractory Period Studies

Atrium: Atropine had no consistent effect on the effective refractory period of the atrium in the 11 patients studied. In nine patients the effect of atropine on the effective refractory period of the atrium was studied at a cycle length of 600 msec. In four (Cases 3, 9, 11 and 14), the effective refractory period decreased by 10 to 20 msec and in three (Cases 2, 5 and 6), it increased by 10 msec; in two patients (Cases 1 and 7), no change occurred.

A–V node: During the control period, the effective refractory period of the A–V node could be determined in only six patients. In the remaining five, the effective refractory period of the atrium was encountered first. Administration of atropine decreased the effective refractory period of the A–V node in all six patients by a mean of more than 51.5 ± 37.3 msec (P <0.001). After atropine, the actual or smallest value for the effective refractory period of the A–V node could not be determined since atrial refractoriness was encountered first in all instances. Figure 2 exemplifies the effect of atropine on the effective refractory period of the A–V node. In all patients atropine shortened the functional refractory period at one or more cycle lengths. The mean value for the functional refractory period of the A–V node was 417.9 ± 10.7 msec during the control period and 371.2 ± 6.4 msec after administration of atropine (P <0.001). The shortening of the functional refractory period after

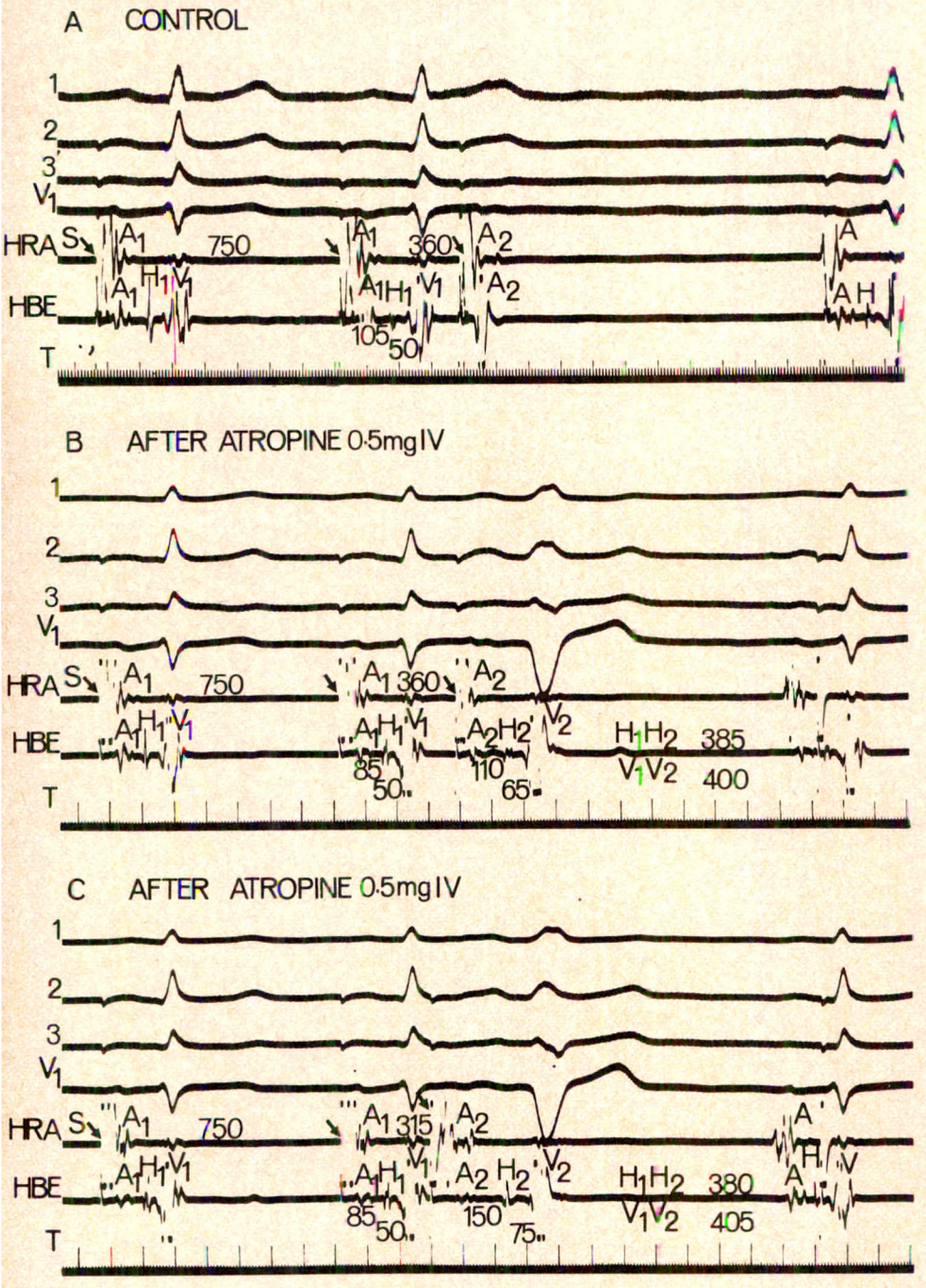

FIGURE 2. Case 1. Effect of atropine on the effective refractory period of the A–V node. In the control period **(panel A)** the effective refractory period of the A–V node is reached at an A_1–A_2 interval of 360 msec. After administration of atropine **(panel B),** the premature atrial beat (A_2) conducts to the ventricle at the same A_1–A_2 interval of 360 msec. The H_1–H_2 interval measures 385 msec and there is aberrant ventricular conduction of a left bundle branch block type with an H_2–V_2 interval of 65 msec. The degree of shortening of the effective refractory period of the A–V node is further exemplified by the fact that conduction to the ventricles occurred at an A_1–A_2 interval of 315 msec **(panel C).** Abbreviations in this and subsequent figures as in Figure 1.

atropine was greater at longer basic atrial cycle lengths.

His-Purkinje system: Atropine in the dose used did not appear to have a direct effect on refractoriness of the His-Purkinje system (Fig. 3). However, H–V prolongation and aberrant ventricular conduction during premature atrial stimulation occurred more frequently after administration of atropine than in the control period, especially at atrial cycle lengths of 700 msec and greater (Fig. 4). This increased frequency was caused by the enhanced A–V nodal conduction induced by atropine which, at any given atrial coupling interval, resulted in an H_1–H_2 interval shorter than that of the control period. The shorter H_1–H_2 interval permitted the impulse of the premature atrial beat to be conducted during the relative refractory period of the His-Purkinje system. In five patients (Cases 1, 2, 6, 7 and 9) the relative refractory period of the His-Purkinje system was encountered after administration of the drug but not before.

Figure 5 is representative of two patients who had no aberrant ventricular conduction when the basic cycle length of atrial stimulation was reduced during

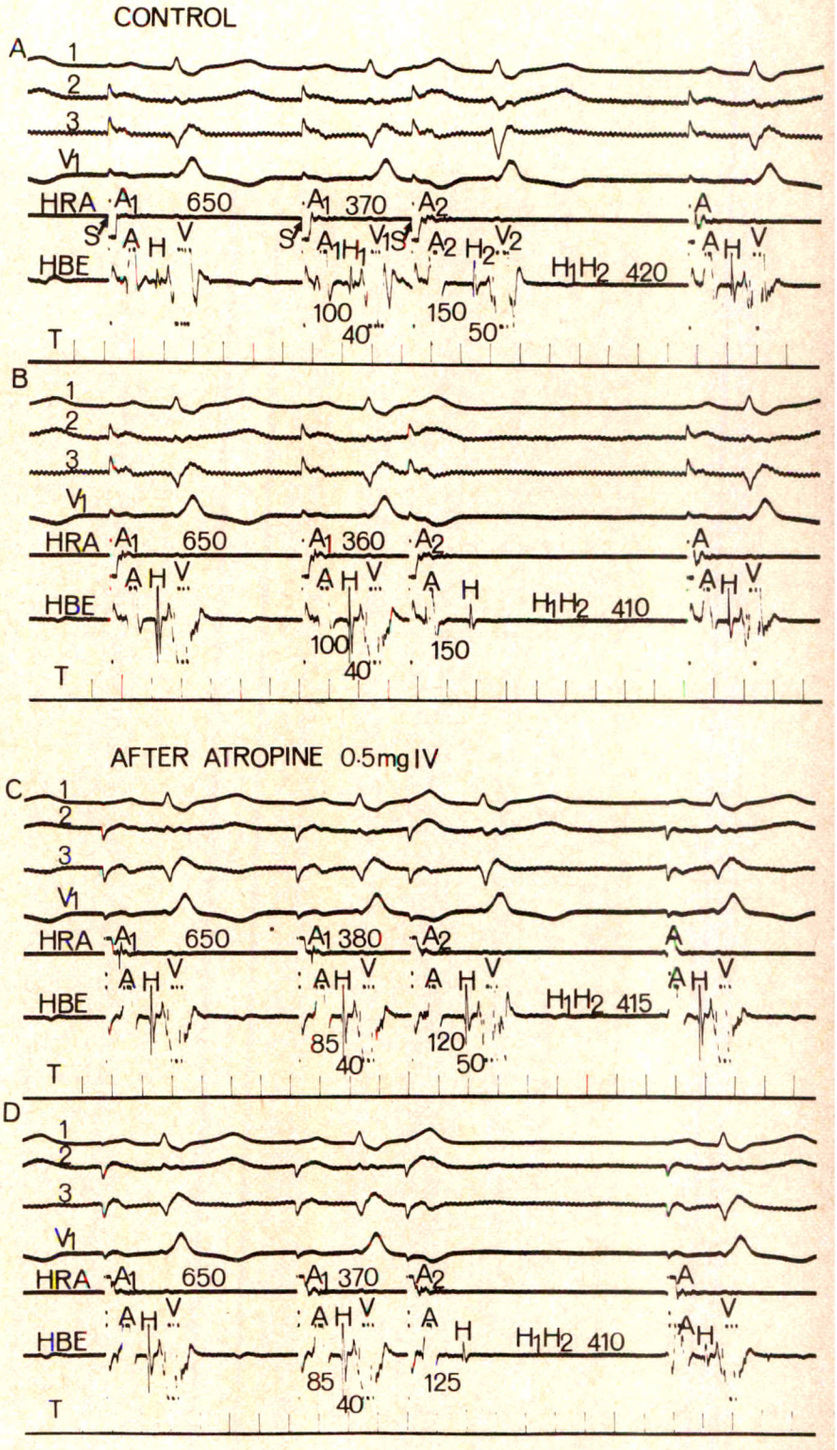

FIGURE 3. Case 14. Effect of atropine on the effective refractory period of His-Purkinje system. In **panels A** through **D** the atrial cycle length is constant at 650 msec. Before administration of atropine, at an A_1–A_2 interval of 370 msec, a premature atrial beat (A_2) conducts to the ventricles with a longer H–V interval (50 msec, **panel A**) than that of the basic drive. The H_1–H_2 interval is 420 msec, which is outside the effective but within the relative refractory period of the His-Purkinje system. By decreasing the A_1–A_2 interval by 10 msec **(panel B)** A_2 reaches the His-Purkinje system during its effective refractory period (410 msec) and blocks within this system. After administration of atropine, A_2 blocks within the His-Purkinje system **(panel D)** at the same H_1–H_2 interval of 410 msec as that of the control period **(panel B).** As shown in **panel C,** A_2 conducted to the ventricles during its relative refractory period (H_2–V_2 interval, 50 msec).

the control period but who manifested aberrant conduction at the shorter cycle lengths after administration of atropine.

In three patients (Cases 2, 3 and 14), at basic atrial cycle lengths of 800, 700 and 550 msec, respectively, the effective refractory period of the His-Purkinje system could be determined only after administration of atropine (Fig. 6 and 7).

In one patient (Case 3) atropine converted a type I gap in A–V conduction[11,13] (Fig. 8) into a type II gap[13] (Fig. 9). In panel B of Figure 8 a relatively late premature atrial depolarization (A_1–A_2 interval 445 msec) is initially blocked

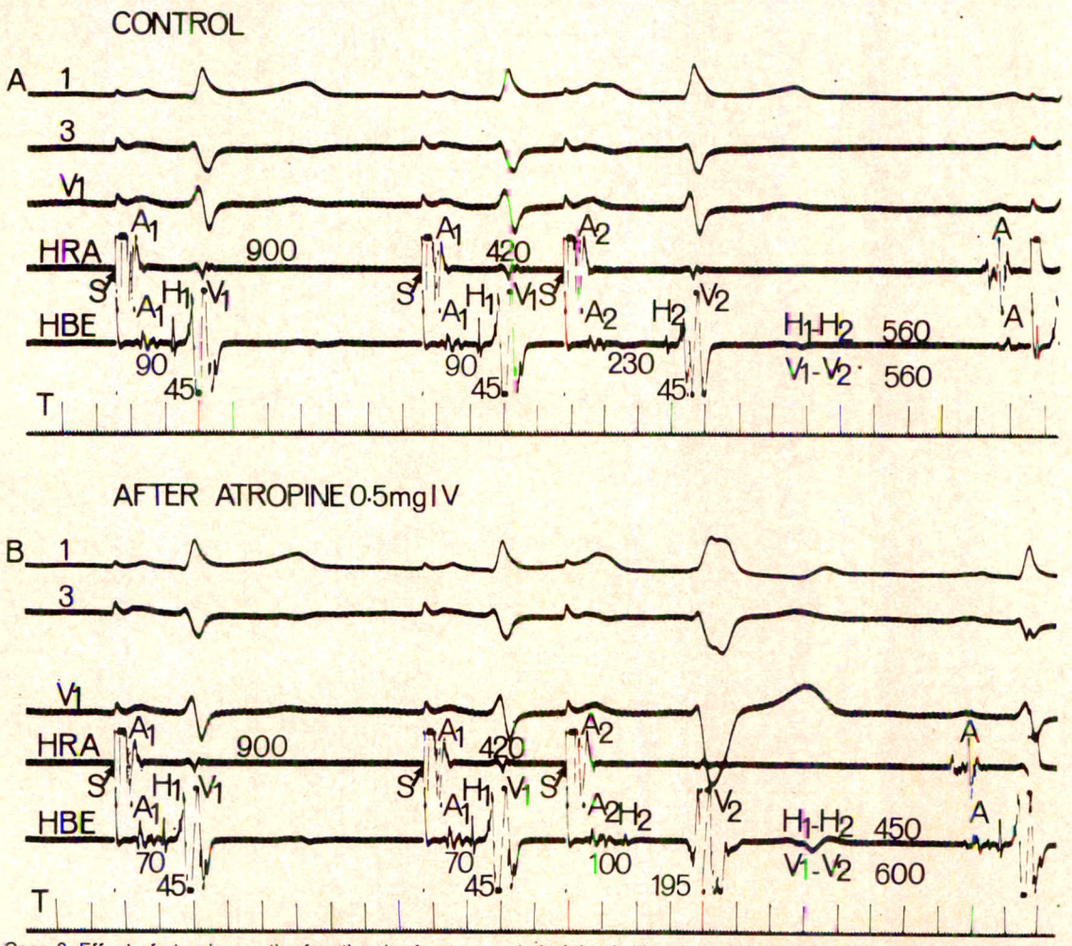

FIGURE 4. Case 3. Effect of atropine on the functional refractory period of the A–V node and the resultant His-Purkinje conduction. Atrial cycle lengths are constant at 900 msec. In the control period **(panel A),** a premature atrial beat (A_2) introduced at an A_1–A_2 interval of 420 msec encounters A–V nodal delay (A_2–H_2 interval 230 msec). The resultant H_1–H_2 interval is 560 msec, and normal ventricular activation occurs with a normal H–V interval of 45 msec. After administration of atropine **(panel B),** the premature atrial beat results in a shorter H_1–H_2 interval (450 msec) caused by enhancement of A–V nodal conduction time (A_2–H_2 interval 100 msec). The premature atrial beat is conducted during the relative refractory period of the His-Purkinje system as evidenced by the markedly prolonged H_2–V_2 interval (195 msec) and aberrant ventricular activation of a left bundle branch block type.

within the His-Purkinje system. The effective refractory period of the His-Purkinje system occurs at an H_1–H_2 interval of 510 msec. In panels C and D, A–V conduction resumes because earlier premature atrial depolarizations encounter greater A–V nodal delay and the resultant H_1–H_2 intervals (545 and 515 msec, respectively) are outside the effective refractory period of the His-Purkinje system.

Figure 9 (same patient) illustrates a type II gap in A–V conduction after administration of atropine. In panel B, a premature atrial impulse (A_2) blocks within the His-Purkinje system at an H_1–H_2 interval of 490 msec. In panel C, an earlier premature atrial depolarization was conducted to the ventricles although the H_1–H_2 interval of 430 msec was less than in panel B. In panel D, block again occurred within the His-Purkinje system when the A_1–A_2 interval was decreased and the resultant H_1–H_2 interval was shortened to 415 msec. This form of gap in A–V conduction has been explained as follows: In panel B, the premature atrial impulse encounters an area of maximal refractoriness within the *distal* His-Purkinje system. In panel C, it encounters conduction delay in the *proximal portion* of the His-Purkinje system which allows recovery of the distal area thereby permitting ventricular excitation. The H_2–V_2 interval is prolonged at 135 msec. In panel D, the premature atrial impulse is again blocked because it encounters the effective refractory period of the proximal portion of the His-Purkinje system.

Discussion

In this study we used a relatively small dose of atropine to avoid marked increases in sinus rate. With larger doses of 1 mg or more, it is not always possible to obtain refractory period studies at comparable cycle lengths before and after administration of the drug. In addition, if significant sinus acceleration were produced by a larger drug dose, the shorter cycle lengths would decrease the relative and effective refractory periods of the His-Purkinje system to such a degree that the indirect effects of atropine on

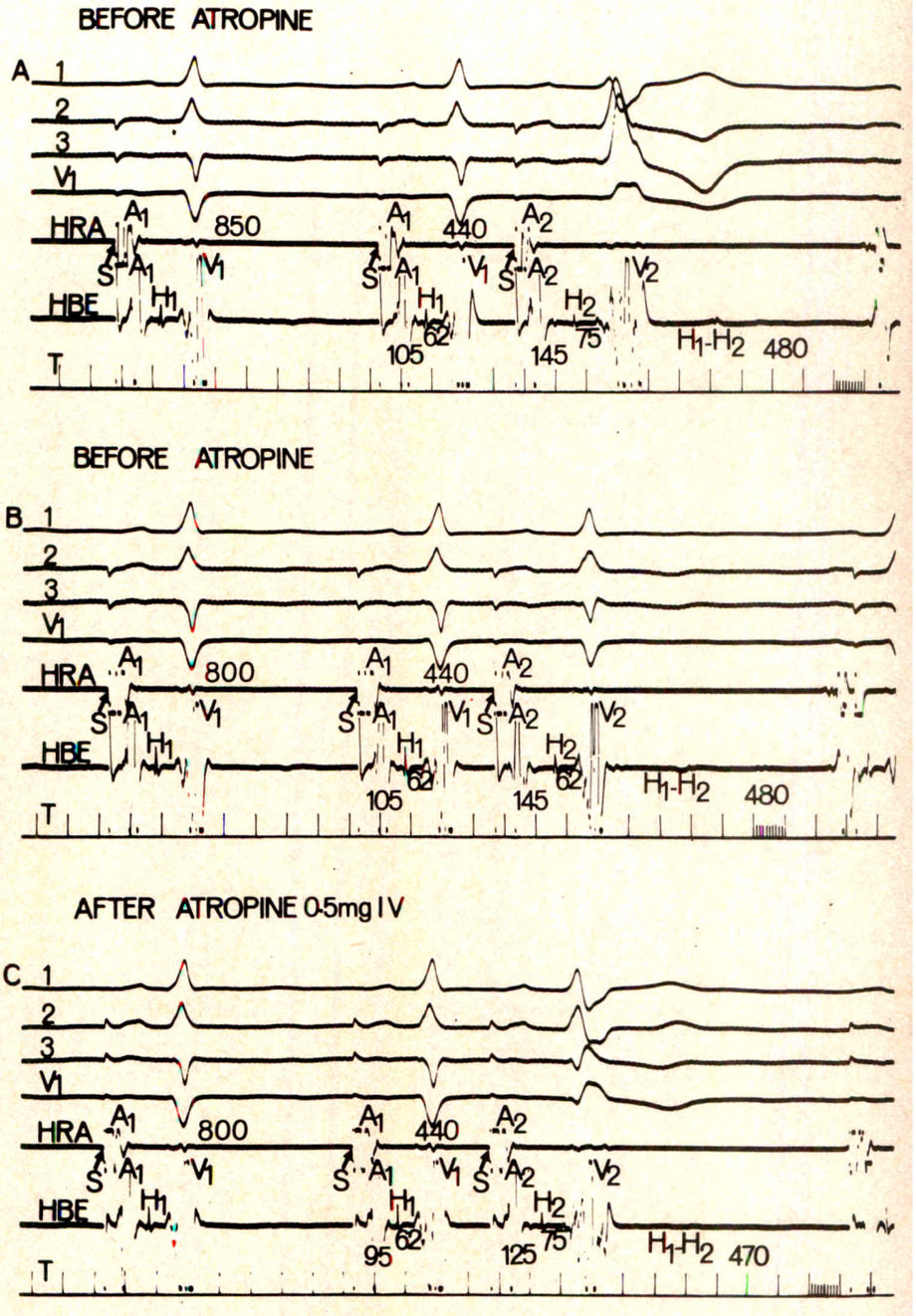

FIGURE 5. Case 2. Aberrant ventricular conduction elicited by atropine. **Panel A:** At a basic cycle length of 850 msec (A_1–A_1) and premature atrial coupling (A_1–A_2) of 440 msec, A_2 conducts to the ventricles aberrantly (right bundle branch block and right axis +120°). The premature atrial beat conducts with a longer H–V (H_2–V_2 75 msec) interval than that of the basic atrial beats (H_1–V_1 interval 62 msec). As shown in **panel B,** decreasing the basic atrial cycle length by 50 msec (A_1–A_1 interval 800 msec) abolishes ventricular aberration and H–V prolongation although the A_1–A_2 and H_1–H_2 intervals are the same in both **panels A** and **B** during the control period. **Panel C:** After administration of atropine, at a basic atrial cycle length (A_1–A_1 interval 800 msec) similar to that of **panel B,** ventricular aberration (right bundle branch block) with H–V prolongation (H_2–V_2 interval 75 msec) resumes. The aberrancy occurs because of a decrease in the functional refractory period of the A–V node (H_1–H_2 470 msec) permitting A_2 to conduct to the His-Purkinje system during its relative refractory period.

these variables would be obscured. We did not observe the initial slowing of sinus rate occasionally seen with administration of atropine.

The well known effects of atropine on the sinoatrial and A–V nodes were observed in all patients. Furthermore, the predictable shortening of both the functional and effective refractory periods of the A–V node was consistently seen.

Atropine appeared to have no direct effect on His-Purkinje conduction time or refractoriness. The greater frequency of His-Purkinje conduction delay, aberrant ventricular conduction and block within the His-Purkinje system after administration of atropine can be explained by the enhanced A–V nodal conduction (shorter A_2–H_2 interval) at a given atrial premature coupling interval, resulting in shorter H_1–H_2 intervals. At these shorter H_1–H_2 intervals the premature atrial impulse entered the His-Purkinje system during its relative or effective refractory period, or both. Thus, atropine may be used to determine the relative (Fig. 2, 4 and 5) and effective (Fig. 6 and 7) refractory periods of the His-Purkinje system in pa-

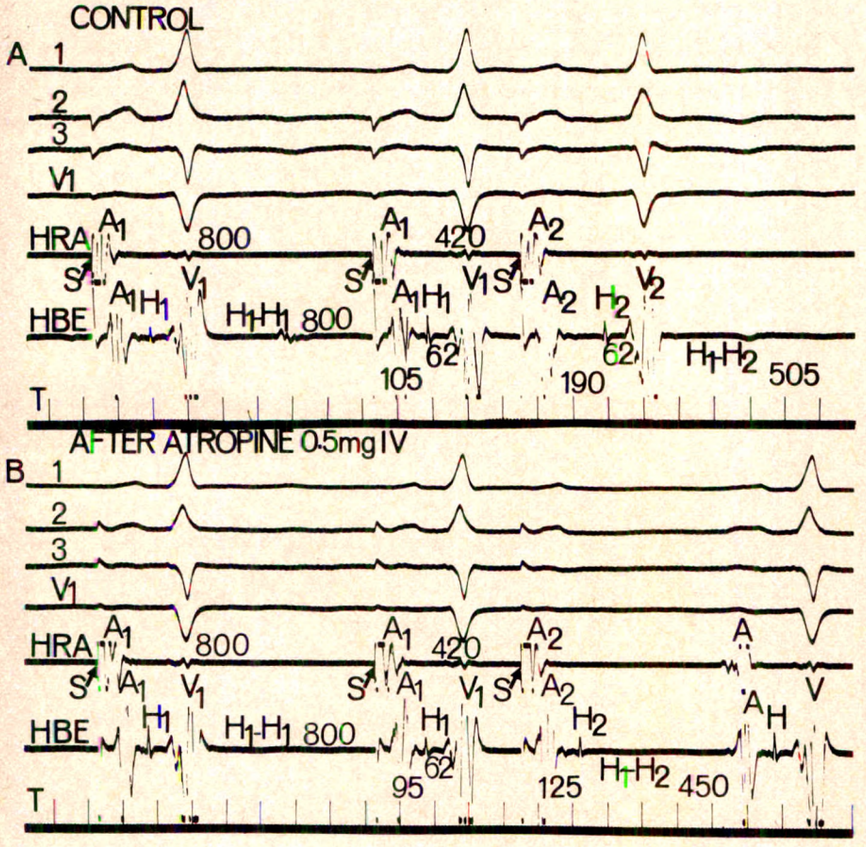

FIGURE 6. Case 2. Effective refractory period of the His-Purkinje system after administration of atropine. In both panels, the atrial cycle length is constant at 800 msec. In **panel A,** A_2 is conducted with a prolonged A–V nodal conduction time (A_2–H_2 interval 190 msec). The resultant H_1–H_2 interval is outside the relative and effective refractory periods of the His-Purkinje system, and therefore normal ventricular activation occurs. As shown in **panel B,** atropine shortens the A–V nodal conduction time of the premature atrial beat (A_2–H_2 interval 125 msec). The resultant H_1–H_2 interval is within the effective refractory period of the His-Purkinje system, and therefore block within this system occurs.

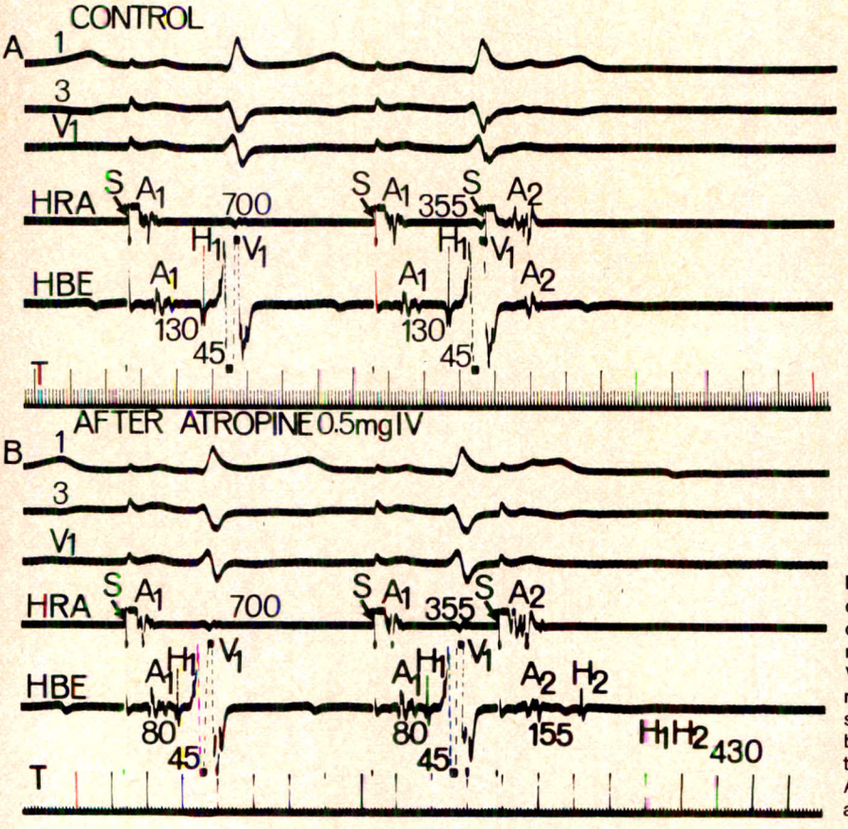

FIGURE 7. Case 3. Effective refractory period of the His-Purkinje system after administration of atropine. At a basic cycle length of 700 msec, the effective refractory period of the A–V node occurred at an A_1–A_2 interval of 355 msec **(panel A). Panel B** shows that atropine shortened A–V nodal conduction of the basic beat (A_1–H_1 80 msec) and the effective refractory period of the A–V node. At the same A_1–A_2 interval (355 msec), A_2 is conducted to and blocked within the His-Purkinje system.

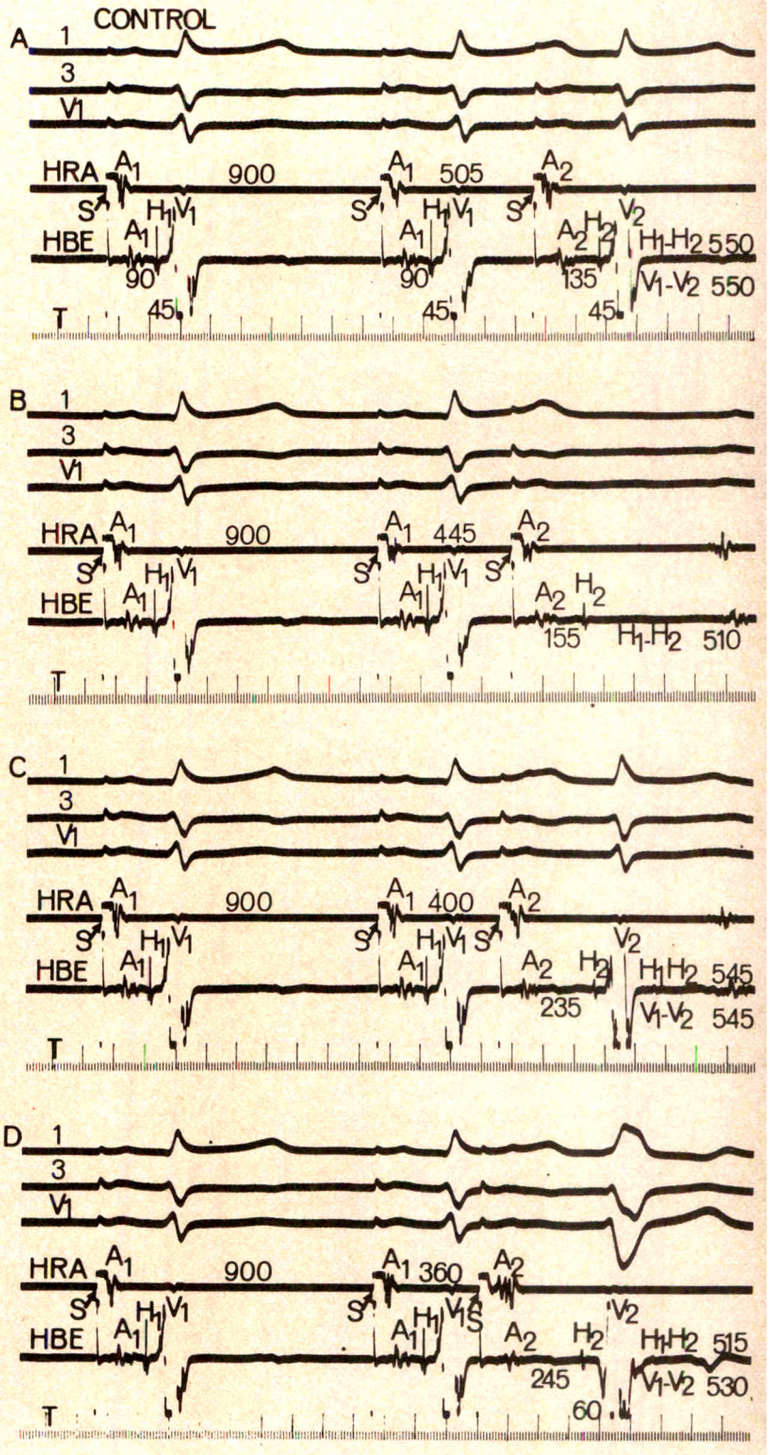

FIGURE 8. Case 3. Typical type I gap in A–V conduction occurred during the control period. The atrial cycle length is constant at 900 msec and the A_1–A_2 interval of the premature beat is progressively decreased in **panels A** through **D.** In **panel B,** the effective refractory period of the His-Purkinje system is reached at an H_1–H_2 interval of 510 msec. Thereafter (**panels c** and **D**), conduction to the ventricles is resumed at shorter A_1–A_2 intervals. The more premature atrial beats encounter greater A–V nodal delay (235 and 245 msec). The resultant H_1–H_2 intervals (545 and 515 msec) are now outside the effective refractory period of the His-Purkinje system, and conduction to the ventricles occurs.

tients who, during control studies, have relatively long functional and effective refractory periods of the A–V node that prevent such determinations.

In most patients the dual actions of atropine (sinus acceleration and enhancement of A–V nodal conduction) occur together. For this reason the drug is generally useful for treating (1) sinus bradycardia with or without first degree heart block, (2) the A–V nodal Wenckebach phenomenon, and (3) some cases of 2:1 A–V nodal block. However, under certain circumstances atropine may increase the severity or shift the site of A–V block. If the electrocardiographic pattern of type I second degree heart block is due to delay in the His-Purkinje system rather than delay in the A–V node, atropine may result in a higher degree of block. The increased severity occurs because (1)

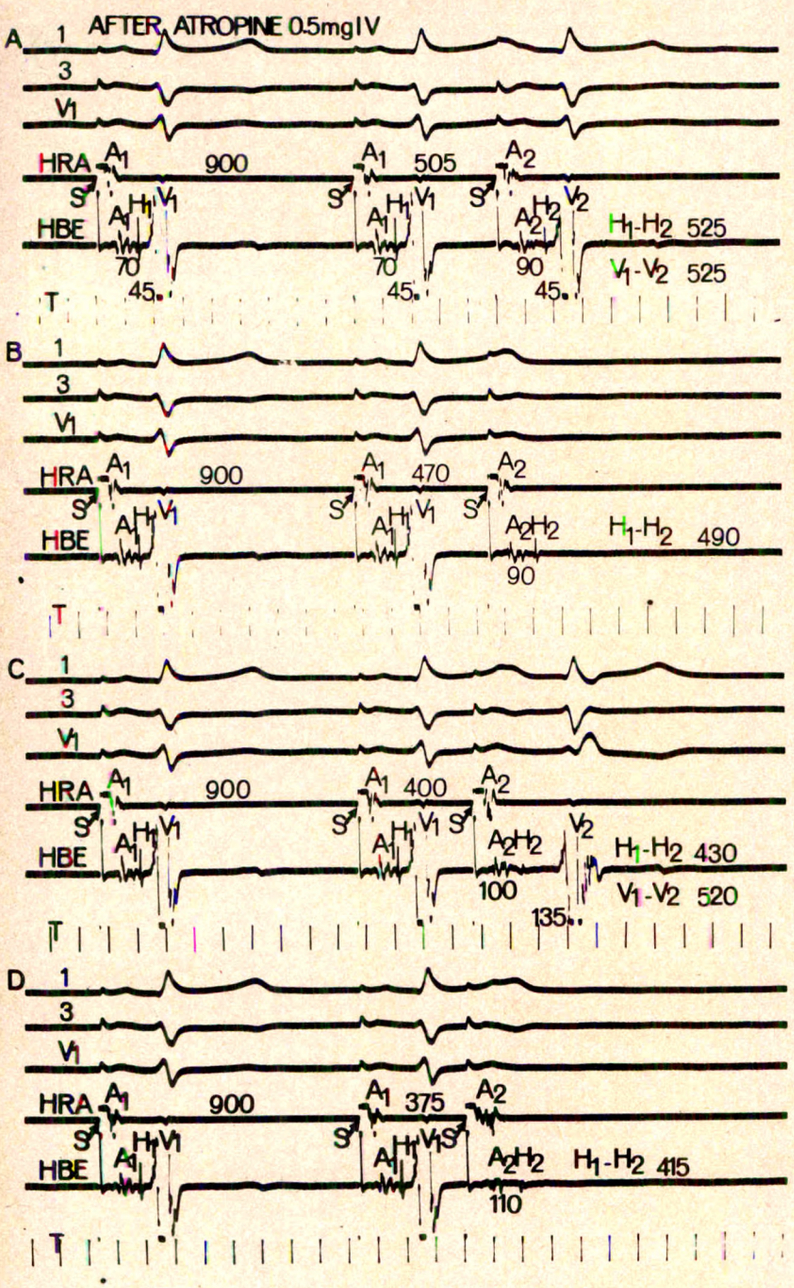

FIGURE 9. Case 3. Atropine converts a type I gap in A–V conduction to a type II gap. Atrial cycle lengths are constant at 900 msec. Atropine shortened A–V nodal conduction time (A_1–H_1 interval) of the basic beat to 70 msec. The premature coupling interval is progressively decreased in **panels A** through **D.** In **panel B,** the effective refractory period of same portion of the His-Purkinje system is reached at an H_1–H_2 interval of 490 msec. In **panel C,** A–V conduction resumes at shorter A_1–A_2 and H_1–H_2 intervals. In **panel D,** the effective refractory period of the His-Purkinje system is again encountered at an H_1–H_2 interval of 415 msec.

sinus acceleration and enhanced A–V nodal conduction result in shorter H–H intervals, and (2) atropine has no direct enhancing effect on His-Purkinje conduction. Figure 7 suggests the possibility that in 2:1 A–V block atropine may change the site of block from the A–V node to the His-Purkinje system. Shift in the site of block is more likely to occur after premature atrial beats. A functional form of 2:1 block below the His bundle was seen more frequently after administration of atropine.[12]

The mechanism involved in type I and type II gaps in A–V conduction have been previously presented.[11,13] The occurrence of gap phenomena depends upon a state of differential refractoriness within the A–V nodal and His-Purkinje systems and does not by itself indicate abnormality in the conducting system. The functional nature of the phenomena is further emphasized by the fact that the conduction gaps may be unmasked by drugs that enhance A–V nodal conduction (Fig. 8 and 9) or obscured by drugs, such as sympathetic beta receptor blocking agents, that prolong A–V nodal conduction.[11]

Acknowledgment

We acknowledge the technical assistance of Stephen Rudich, PhD, Audrey Pederson and Mary Vecchione.

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Effects of Digoxin on Atrioventricular Conduction Patterns in Man

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Digoxin was acutely administered to 17 patients, and its effects on atrioventricular (A–V) conduction were assessed. In the control state, before administration of digoxin, progressively premature atrial depolarization showed conduction delay and block confined solely to the A–V node in eight patients and to both the A–V node and the more distal His-Purkinje tissue in nine patients. His-Purkinje conduction delay was manifested on the surface electrocardiogram by ventricular aberration. After administration of digoxin, an early atrial premature impulse either was blocked in the A–V node or reached the distal intraventricular conduction system so late that block or conduction delay below the His bundle was reduced or no longer occurred. Ventricular aberration on the surface electrocardiogram was thus reduced or eliminated. These effects of digoxin on A–V conduction were due to its effect on the A–V node of slowing conduction of a premature impulse. Such action on the A–V node may abolish aberrant ventricular conduction in atrial fibrillation.

This clinical investigation was undertaken to study the effects of acutely administered digoxin on the conduction of an impulse from the atria to the ventricles. With use of His bundle electrograms obtained by the catheter technique,[1,2] atrioventricular (A–V) conduction time may be subdivided into its component parts. Thus, the time required for an impulse to pass through the A–V node may be separated from the time required for the impulse to traverse the more distal intraventricular His-Purkinje system.[3–5] With the introduction of properly timed premature atrial depolarizations, an atrial impulse will be delayed to various degrees or blocked in the A–V node or His-Purkinje system. The patterns of conduction delay and block of premature atrial depolarizations may be grouped and studied.[6–10] It is known from studies of the surface electrocardiogram that digoxin delays A–V conduction. However, use of His bundle electrograms permits the site of action of this commonly used cardiac glycoside to be more discretely localized to the A–V node or the His-Purkinje system and allows investigation of the alterations in A–V conduction patterns.

Methods

Seventeen subjects ranging in age from 21 to 63 years were studied in the postabsorptive, nonsedated state. All subjects had normal P–R intervals. Diagnoses of heart disease (Table I) were made by history and physical examination. Informed consent was obtained in all cases.

Recording techniques: With the patient under local anesthesia, a no. 7 tripolar catheter was introduced percutaneously into a femoral vein and fluoroscopically positioned across the tricuspid valve to record electrograms from the atrium, His bundle and ventricle.[1,2] These electrograms were displayed oscillographically on a multichannel recorder (Electronics for Medicine) within a frequency range of 40 to 500 Hz. A second bipolar catheter, used to

From the Cardiopulmonary Laboratory, U. S. Public Health Service Hospital, Staten Island, N. Y. This work was supported in part by the Federal Health Program Service, U. S. Public Health Service Project Py 73-1 and National Heart and Lung Institute Project HE 12536-04. Manuscript accepted July 11, 1973.

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TABLE I

Effects of Digoxin on the A–V Conduction System (msec)

Case no.	Age (yr) & Sex	Diagnosis	A–V Conduction System: FRP V_1–V_2 Pre	Post	Δ	ERP A_1–A_2 Pre	Post	Δ	A–V Node: FRP H_1–H_2 Pre	Post	Δ	ERP A_1–A_2 Pre	Post	Δ	Ventricular Specialized Conducting System: ERP H_1–H_2 Pre	Post	Δ
Group I (Patients with Conduction Delay or Block of a Premature Impulse in A–V Node During Control State)																	
1	44M	NHD	390	430	+40	260	370	+110	390	430	+40	260	370	+110	...	...	...
2	38M	NHD	500	510	+10	430	450	+20	500	510	+10	430	450	+20	...	...	...
3	58F	ASHD	530	550	+20	280	330	+50	530	550	+20	280	330	+50	...	...	...
4	21M	NHD	500	510	+10	430	450	+20	500	510	+10	430	450	+20	...	...	...
5	30M	ASHD	350	370	+20	270	300	+30	350	370	+20	270	300	+30	...	...	...
6	63M	ASHD	370	380	+10	280	290	+10	370	380	+10	280	290	+10	...	...	...
7	55M	ASHD	370	400	+30	300	330	+30	370	400	+30	300	330	+30	...	...	...
8	34M	ASHD	390	450	+60	350	370	+20	390	450	+60	350	370	+20	...	...	...
Group II (Patients with Conduction Delay or Block of a Premature Impulse in Both A–V Node and His-Purkinje System During Control State)																	
9	42M	NHD	370	380	+10	290	310	+20	350	380	+30	290	310	+20	...	...	...
10	39M	NHD	410	450	+40	340	400	+60	390	450	+60	340	400	+60	...	...	...
11	57M	ASHD	400	420	+20	330	340	+10	370	420	+50	330	340	+10	...	...	...
12	60M	HCVD	390	410	+30	300	320	+20	370	410	+40	300	320	+20	...	...	...
13	56M	HCVD	430	450	+10	330	345	+15	420	430	+10	330	345	+15	...	...	...
14	45F	ASHD	310	320	+10	<220	<220	A.R.	280	290	+10	<220	<220	A.R.	...	...	...
15	44M	ASHD	390	380	−10	330	300	−30	350	360	+10	260	280	+20	380	380	0
16	42M	ASHD	370	370	0	320	330	+10	320	330	+10	<260	>260	*	340	340	0
17	28F	NHD	390	430	+40	335	380	+50	370	430	+60	295	380	+85	380	...	†

*Increased.

†Effective refractory period of the ventricular specialized conducting system was not reached because of block in the atrioventricular node.

A.R. = atria refractory; ASHD = arteriosclerotic heart disease; ERP = effective refractory period; FRP = functional refractory period; HCVD = hypertensive cardiovascular disease; NHD = no heart disease; Post = 30 to 45 minutes after intravenous administration of 0.75 mg of digoxin; Pre = before administration of digoxin.

stimulate the right atrium, was introduced percutaneously into a right antecubital vein and positioned fluoroscopically against the right lateral atrial wall. Standard electrocardiographic leads I, II, III, V_4 and V_6 were routinely recorded. Careful attention was paid to the grounding of all equipment.

Experimental procedure: The effects of a single premature atrial depolarization on A–V conduction were assessed before and 30 to 45 minutes after intravenous administration of 0.75 mg of digoxin.

The basic driving stimulus (S_1) and test stimulus (S_2) were delivered to the right atrium from Tektronix 160 series wave form and pulse generators and were suitably isolated from ground (Bioelectric Instruments type ISB). S_1, a 2 msec rectangular pulse twice diastolic threshold, was delivered to the atrium at a rate slightly faster than sinus rate. S_2, a 2 msec rectangular pulse three to four times diastolic threshold, was introduced by way of the same electrode after every 10th driving stimulus. By decreasing the S_1–S_2 interval in 5 to 10 msec decrements the entire atrial cycle was scanned.

Measurements: The A–V interval, measured on the His bundle electrogram from the onset of the atrial and ventricular deflections, was used to approximate total A–V conduction time. The A–H interval, measured from the onset of the atrial deflection to the onset of the His bundle deflection, was used to approximate A–V nodal conduction time. The H–V interval, measured from the onset of the His bundle deflection to the onset of the ventricular deflection, represented conduction time through the His bundle and remaining ventricular specialized conduction system. The A_1–A_2, H_1–H_2 and V_1–V_2 intervals were measured from the onset of the atrial, His bundle and ventricular deflections, respectively, of the last basic drive beat to the onset of the corresponding deflection of the premature atrial depolarization. Conduction delay in the ventricular specialized conduction system could be localized to the right or left bundle branch by detecting bundle branch block patterns on standard electrocardiographic recordings.

Definitions

The effective refractory period of the A–V conduction system was defined as the longest A_1–A_2 interval at which the atrial test response (A_2) failed to conduct to the ventricles. The effective refractory period of the A–V node was

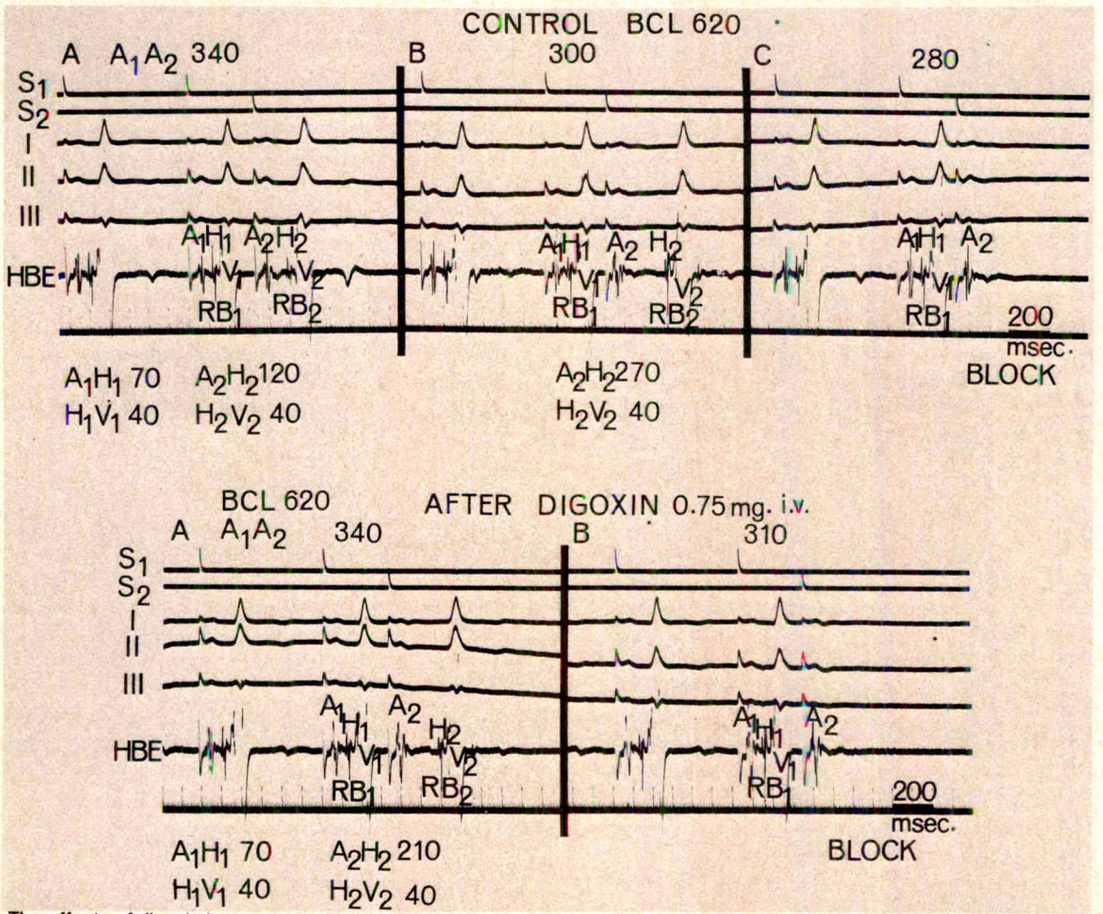

FIGURE 1. The effects of digoxin in a patient in Group I (delay of a premature impulse occurring solely in the A–V node during the control state). S_1 is the basic driving stimulus and S_2 is the premature stimulus. BCL = basic drive cycle length. I, II and III = standard electrocardiographic leads. HBE = His bundle electrogram. Time lines are indicated and values are in milliseconds. A_1, H_1, RB_1 and V_1 represent, respectively, atrial, His bundle, right bundle branch and ventricular depolarizations during the basic response. Those letters with subscript 2 represent depolarizations during the premature response. A_1A_2 is the time between basic and premature atrial depolarizations; A–H is an approximation of A–V conduction time and H–V is conduction time in the His-Purkinje system. Before administration of digoxin **(upper panels A, B and C),** as the introduced atrial depolarization is made progressively more premature, conduction time through the A–V node increases in a graded fashion from 120 **(panel A)** to 270 msec **(panel B).** In **panel C,** when A_2 is even more premature (A_1–A_2 interval 280 msec) A_2 is blocked above the His bundle within the A–V node. In this patient during premature atrial stimulation ventricular aberration was not seen nor was the H_2–V_2 interval prolonged. Thirty minutes after intravenous administration of 0.75 mg of digoxin **(lower panels A and B),** conduction time of a premature impulse through the A–V node is slowed. At an A_1–A_2 interval of 340 msec **(lower panel A),** the A_2–H_2 interval is 210 msec and represents a 90 msec increase compared to the value before digoxin at the same A_1–A_2 interval **(upper panel A).** Block above the His bundle, within the A–V node, now occurs at an A_1–A_2 interval of 310 msec **(lower panel B);** before digoxin, block first occurred at an A_1–A_2 interval of 280 msec. Conduction time through the His-Purkinje system remains unchanged.

considered the longest A_1–A_2 interval at which the atrial test response (A_2) failed to conduct to the His bundle.

The effective refractory period of the ventricular specialized conduction system was indicated by the longest H_1–H_2 interval at which the His bundle test response (H_2) failed to propagate to the ventricles.

The functional refractory period[11] *of the A–V conduction system* was defined as the minimal interval between two successive ventricular responses (V_1–V_2) propagated from the atrium,[12,13] and the functional refractory period of the A–V node, the minimal interval between two successive His bundle responses (H_1–H_2) propagated from the atrium.[14]

The relative refractory period of the A–V node was considered to begin when conduction of a premature atrial depolarization through the A–V node was first delayed. The relative refractory period of the ventricular specialized conduction system was considered to begin when conduction of a premature atrial depolarization through the His-Purkinje tissue was first delayed or when aberrant ventricular depolarization was observed on the surface electrocardiograms, or both.

Results

Effects of digoxin in Group I: The A–V conduction pattern in which conduction delay and block of a premature atrial impulse was confined solely to the A–V node was found during the control period (before administration of digoxin) in 8 of 17 patients studied (Group I, Table I). This delay appeared on

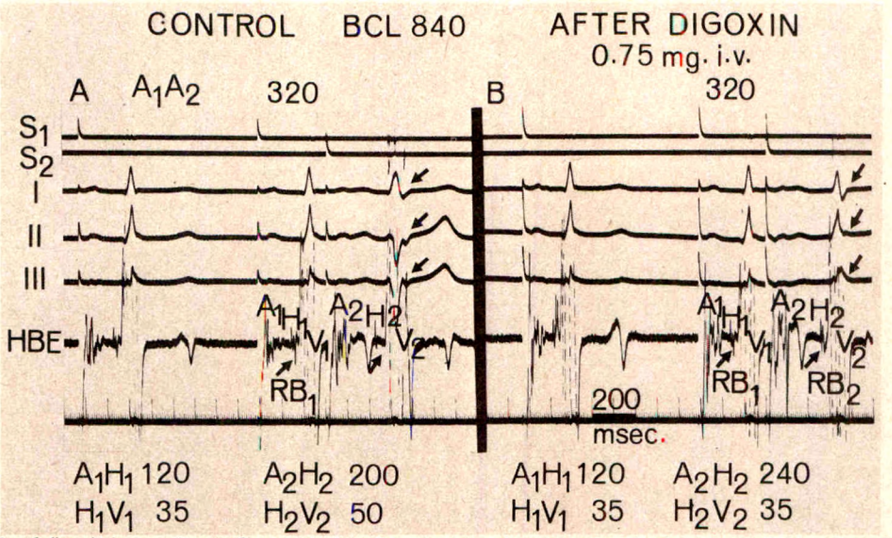

FIGURE 2. The effects of digoxin in a patient in Group II (delay of a premature impulse occurring in both the A–V node and His-Purkinje system). Abbreviations as in Figure 1. **Arrows** pointing to standard leads I, II and III emphasize changes in ventricular aberration after drug administration. In **panel A,** before digoxin, A–V nodal conduction time (A_2–H_2 interval) is 200 msec when the atrium is prematurely depolarized at an A_1–A_2 interval of 320 msec. This conduction delay in the A–V node is not sufficient to prevent the premature atrial depolarization from reaching the His-Purkinje system during its refractory period. Conduction time through the His-Purkinje system is thereby delayed as evidenced by the H–V interval, which increases from 35 msec during basic drive (H_1–V_1 interval) to 50 msec during premature stimulation (H_2–V_2 interval). The right bundle branch potential is absent, and ventricular aberration **(arrows)** probably represents right bundle branch and left anterior hemiblock.

In **panel B,** after intravenous administration of 0.75 mg of digoxin, A–V nodal conduction time is increased 40 msec (A_2–H_2 interval 240 msec) for the same premature atrial interval (A_1–A_2 interval 320 msec) shown in **panel A.** The delay in A–V nodal conduction allows the distal His-Purkinje system to recover more completely from the preceding impulse and to be less refractory. Thus, there is no evidence of conduction delay in the His-Purkinje system on the basis of the H_2–V_2 interval, which decreases to 35 msec, a value identical to that of the basic drive (H_1–V_1). The right bundle branch potential is now present in the premature response. Ventricular aberration on the surface electrocardiogram is clearly reduced. The S wave in lead I may indicate refractoriness of the more distal right bundle branch.

the surface electrocardiogram as an increased P–R interval of the premature beat with a corresponding increase in the R–R interval of the basic and premature beats. Examination of the His bundle electrograms obtained from these patients showed that A–V nodal conduction time of the premature beat (A_2–H_2 interval) increased progressively as the atrial depolarization became increasingly more premature (Fig. 1, upper panels A and B). When atrial depolarization was sufficiently premature, block above the His bundle occurred (Fig. 1, upper panel C). The H–V interval, which approximates conduction time through the His-Purkinje system, remained unchanged at all premature intervals because conduction through the more proximal A–V node was sufficiently slow to allow the more distal His-Purkinje system time to recover from the preceding impulse. Conduction of the premature impulse to the ventricles with aberration of the QRS complex on the surface electrocardiogram was uncommon in these patients.

Because the A–V node was the component of the A–V conduction system most refractory to the conduction of a premature impulse, the relative, functional and effective refractory periods of the A–V conduction system were determined by the refractory properties of the A–V node. Thus, the eight patients in this group had identical values for the functional and effective refractory periods of the A–V node and the A–V conduction system (Table I).

After administration of digoxin, conduction of an atrial depolarization through the A–V node was slowed, but conduction through the His-Purkinje system was unaffected. A–V nodal conduction time was increased compared to the control value at the same A_1–A_2 interval (Fig. 1, lower panel A). No change in the H–V interval was noted. After digoxin, block above the His bundle occurred at an A_1–A_2 interval longer than that of the control response (Fig. 1, lower panel B). In addition, there was an equal increase in refractoriness of the A–V node and the A–V conduction systems in all eight patients in this group (Table I). Therefore, digoxin acted solely on the A–V node to slow conduction of a premature impulse, thereby altering the pattern of A–V conduction.

Effects of digoxin in Group II: In this group of nine patients, conduction delay or block of a premature impulse, or both, occurred in both the A–V node and the His-Purkinje system during the control period (Group II, Table I; Fig. 2 and 3). Because conduction of the premature impulse through the A–V node was faster than in patients in Group I, the impulse reached the His-Purkinje tissue when this tissue was partially refractory. Therefore, conduction through the His-Purkinje system was delayed and the H_2–V_2 interval was prolonged (Fig. 2A and 3, A and B). The surface electrocardiogram showed conduction of the premature impulse to the ventricles with aberration of the QRS complex. In 5 patients in this group (Pa-

tients 9 to 13) the A–V node was the most refractory component of the A–V conduction system, and a sufficiently premature impulse was blocked first in the A–V node. In the remaining 4 patients (Patients 14 to 17) the His-Purkinje system was the most refractory component, and block below the His bundle occurred before block in the A–V node (Fig. 3C). In all of these latter 4 patients, when the impulse was even more premature, block also occurred in the A–V node (Fig. 3D).

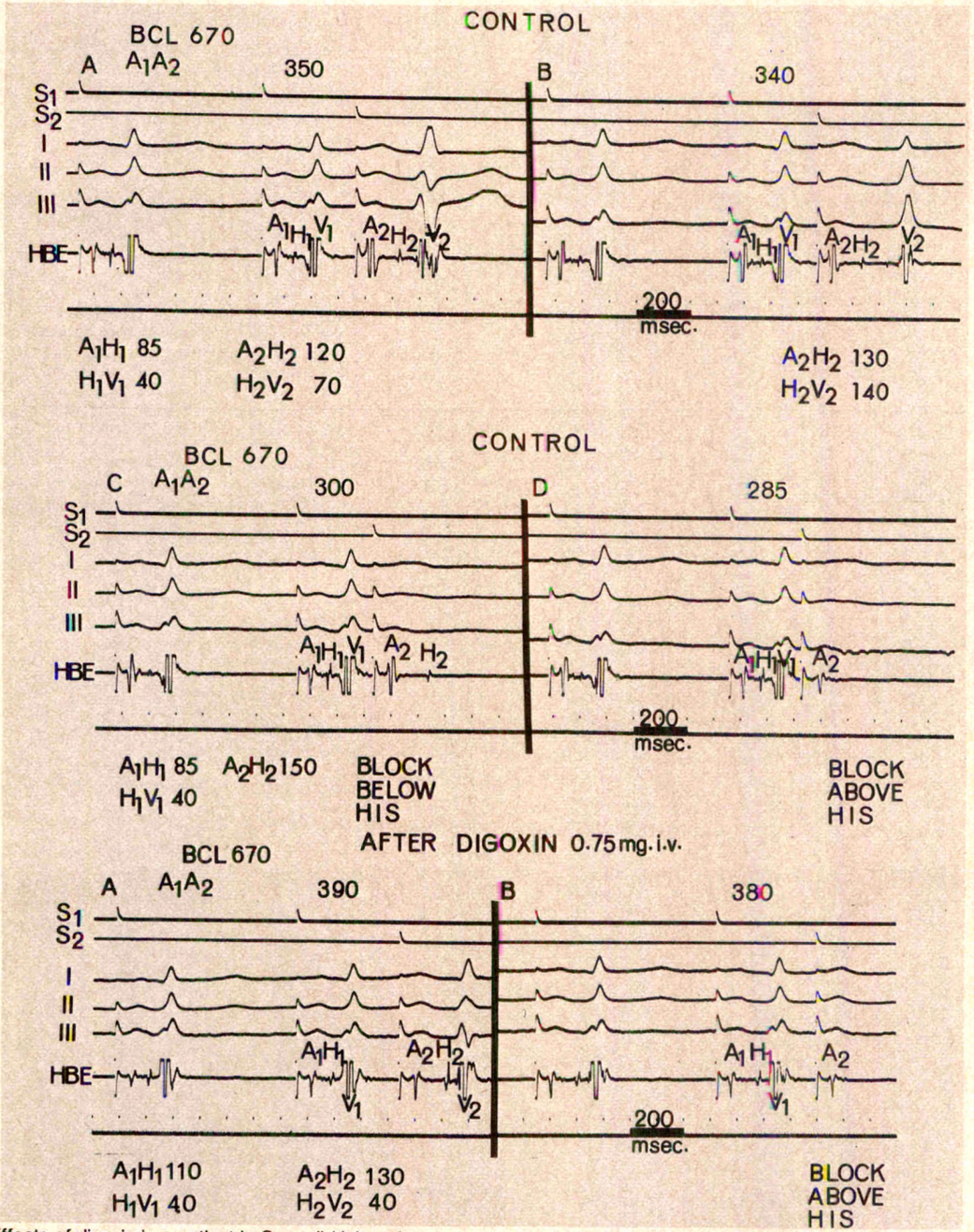

FIGURE 3. Effects of digoxin in a patient in Group II (delay of a premature atrial depolarization occurring in both the A–V node and His-Purkinje system and block occurring first below the His bundle during the control state). Abbreviations as in Figure 1. **Panels A** through **D** are recordings obtained before administration of digoxin. In **panel A**, at an A_1–A_2 interval of 350 msec, the A–H interval increases from 85 (A_1–H_1 interval) to 120 msec (A_2–H_2 interval) and the H–V interval from 40 (H_1–V_1 interval) to 70 msec (H_2–V_2 interval), indicating conduction delay in both the A–V node and His-Purkinje system. In **panel B**, at a more premature A_1–A_2 interval of 340 msec, the A_2–H_2 interval increases to 130 msec and the H_2–V_2 interval to 140 msec. Ventricular aberration is present in lead V_2 in both **panels A** and **B**. In **panel C**, at an A_1–A_2 interval of 285 msec, block occurs above the His bundle within the A–V node. After digoxin, A–V nodal conduction time increases from 85 (A_1–H_1 interval) to 110 msec (A_1–H_1 interval) at the same basic driving cycle length of 670 msec. In **panel A** (after digoxin), at an A_1–A_2 interval of 390 msec, the H_2–V_2 interval is 40 msec and ventricular aberration is minimal. In **panel B** (after digoxin), at an A_1–A_2 interval of 380 msec, block first occurs above the His bundle within the A–V node.

After administration of digoxin, in 6 patients in this group (Patients 9 to 14), conduction delay and block of a premature impulse were confined solely to the A–V node, and neither conduction delay nor block occurred in the His-Purkinje system (Fig. 2B and 3, lower panel A). Digoxin now slowed A–V nodal conduction sufficiently to allow the His-Purkinje system time to recover from the preceding impulse. Aberrant ventricular conduction of a premature impulse was reduced (Fig. 2B). The effective and functional refractory periods of the A–V node and A–V conduction system were identical after digoxin and were increased from pre-digoxin levels. In the remaining 3 patients, (Patients 15 to 17) A–V nodal conduction delay of a premature impulse was increased after digoxin, but not enough to prevent the impulse from reaching the His-Purkinje system outside its refractory period. Consequently, in Patients 15 and 16 block still occurred in the His-Purkinje system, and in Patient 17 delay in the His-Purkinje system preceded A–V nodal block. Digoxin had no apparent direct effect on conduction through the His-Purkinje system.

Discussion

The acute effects of digoxin on A–V conduction patterns in man depend primarily on the sensitivity of the A–V node to the cardiac glycoside. These effects of digoxin are related to delayed A–V nodal conduction[14–16] as a result of increased A–V nodal refractoriness.[12,17,18] Mendez and Mendez[19] found that ouabain and digitoxin in dogs increased refractoriness of the A–V conduction system to the point of complete A–V block. However, the response patterns were not detailed in their study, and His bundle electrograms were not available to localize more precisely the site of action of digitalis.

Clinically, the effects of digitalis on cardiac conduction during sinus rhythm may be unmasked by right atrial pacing[20]; on other occasions these effects may be readily manifested by a prolonged P–R interval.[21] Typically, a prolonged QRS complex has not been observed after administration of digitalis.[22,23] In these latter studies digoxin did not affect the His-Purkinje tissue directly to delay intraventricular conduction. Hoffman and Singer[14] found no direct evidence in man that digoxin affects refractoriness of the His-Purkinje system. However, in our studies digoxin did appear to have an indirect effect on conduction of a premature impulse through the His-Purkinje system. Digoxin, by prolonging A–V nodal conduction time, permitted the premature impulse to arrive at His-Purkinje tissue when this tissue was less refractory. Ventricular aberration was thereby reduced or eliminated. The elimination of ventricular aberration in dogs by delaying conduction of a premature atrial impulse in the A–V node with vagal stimulation has also been noted.[24]

After administration of digoxin in Patient 15, there was a paradoxical decrease in refractoriness of the A–V conduction system; that is, a ventricular response, V_2, could be elicited at a shorter A_1–A_2 interval after digoxin. This occurred because the increase in A–V nodal conduction time after digoxin allowed the ventricular specialized conduction tissue time to recover partially from its refractory state. Thus, after digoxin the net effect was a decrease in refractoriness of the A–V conduction system. This was the only case in which this phenomenon occurred.

In conclusion, the effect of acute intravenous administration of digoxin on A–V conduction was studied in 17 unsedated subjects. During the control period, conduction delay of a premature atrial impulse occurred solely in the A–V node in eight subjects (Group I) and occurred in both the A–V node and the His-Purkinje system in nine subjects (Group II). Because digoxin slowed conduction in the A–V node, a premature atrial depolarization could be prevented from reaching the His-Purkinje system during its refractory state and thus ventricular aberration was reduced or eliminated. Patterns of A–V conduction were altered. Clinically, digoxin may abolish aberrant ventricular conduction in atrial fibrillation by increasing A–V nodal refractoriness and thereby enhancing concealment within the A–V node. Digoxin in the dosage used did not affect refractoriness in the His-Purkinje system at the time of study (30 minutes after administration). In one subject, after administration of digoxin, a paradoxical decrease in refractoriness of the A–V conduction system was observed at a time when refractoriness in the A–V node increased.

Acknowledgment

We acknowledge the assistance of Anne Mazzella, Audrey Pedersen, Mary Vecchione, Joan Olsen, Michael Moretti, and Kenneth Donohue.

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Diagnostic Value of Clinical History, Exercise Testing and Atrial Pacing in Patients with Chest Pain

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The clinical history and the electrocardiographic response to graded exercise testing and atrial pacing were correlated with the presence or absence of severe coronary artery disease, as demonstrated by coronary angiography, in 70 patients. A clinical history of angina pectoris was a very sensitive (90 percent) but less specific (80 percent) predictor of severe coronary artery disease. Ischemic S–T segment depression greater than or equal to 1 mm was the most accurate electrocardiographic predictor. When this criterion was used, the graded exercise test was less sensitive (65 vs. 72 percent) but more specific (83 vs. 70 percent) than atrial pacing. Results of a discriminant function analysis of several possible predictors of severe coronary artery disease indicated that atrial pacing does not contribute significantly to the diagnosis in patients submitted to a graded exercise test.

Exercise electrocardiography is a well accepted method of detecting coronary insufficiency in patients with a history of chest pain. The relation between horizontal and downsloping S–T segment depressions and the presence of severe coronary artery disease has been assessed in follow-up mortality studies.[1,2] More recently, these S–T segment changes were correlated with anatomic findings at coronary angiography.[3–6] Atrial pacing was introduced as another method of determining the anginal threshold.[7] By increasing the oxygen consumption of the heart, this procedure can precipitate angina pectoris and provoke ischemic S–T segment changes.

No studies are available comparing the value and limitations of exercise testing and atrial pacing in determining the presence or absence of severe coronary artery disease. In this study we compared the value of these two stress tests in predicting severe coronary artery disease in patients with chest pain. In addition, some clinical and electrocardiographic data were combined in an attempt to improve the predictive value. Finally, the additional independent contribution of various diagnostic variables was determined.

Methods

Selection of patients: Seventy patients (59 men and 11 women, aged 30 to 61 years [mean 47.2 years]) with a history of chest pain warranting coronary angiography were studied. Patients with congenital, hypertensive or rheumatic heart disease, intermittent claudication or a cardiothoracic ratio of more than 0.5 were excluded. Treatment with digitalis, quinidine, procainamide or beta adrenergic blocking agents was also a criterion for exclusion.

After the initial clinical history was obtained, the patients were classified as having typical angina pectoris or atypical chest pain. The former diagnosis was exclusively reserved for patients complaining of pain, pressure or constriction in the anterior area of the chest, usually precipitated by effort and relieved within 10 minutes by rest.

All patients with electrocardiographic findings at rest that were definitely abnormal except for discrete S–T wave changes were excluded from the study. Q waves were classified according to the Minnesota code,[8] and pa-

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TABLE I

Clinical History, Exercise Testing and Atrial Pacing Correlated with the Presence or Absence of Severe Coronary Artery Disease

	Group I* (40 patients)	Group II† (30 patients)
I. Clinical history		
Atypical chest pain	4	24
Angina pectoris	36	6
II. Graded exercise test		
A. Ischemic S–T segment depression during exercise (mm)		
<0.5	16	24
0.5–0.9	0	3
1–1.9	8	1
2–2.9	7	0
3–3.9	4	2
⩾4	5	0
B. Ischemic S–T segment depression after exercise (mm)		
<0.5	18	22
0.5–0.9	2	3
1–1.9	12	3
2–2.9	5	2
3–3.9	2	0
⩾4	1	0
C. Maximal heart rate (beats/min)		
<100	4	0
100–119	8	3
120–139	14	2
140–159	10	8
160–179	3	12
⩾180	1	5
D. Angina induced by exercise		
Present	28	3
Absent	12	27
III. Atrial pacing		
A. Ischemic S-T segment depression (mm)		
<0.5	11	19
0.5–0.9	0	2
1–1.9	10	4
2–2.9	12	3
3–3.9	6	2
⩾4	1	0
B. Maximal heart rate (beats/min)		
120–139	8	3
140–159	17	8
160–179	9	13
⩾180	6	6
C. Angina pectoris, induced by pacing		
Present	30	3
Absent	10	27

* Group I = severe coronary artery disease determined angiographically.

† Group II = normal coronary arteries or minor lesions.

tients with Q waves classified between codes 1-1-1 and 1-2-8 were considered to have old myocardial infarction and excluded from the study.

Routine laboratory data were obtained in each patient; patients with anemia or abnormal hepatic or renal function were excluded. Serum cholesterol was determined according to the method of Pearson.[9] The graded exercise test, the atrial pacing test and selective coronary angiography were performed on 3 consecutive days, at least 2 hours after a light meal.

Graded exercise test: This test was performed on a calibrated bicycle ergometer (Elema-Schönander AM 368). The electrodes were attached to the patient sitting on the ergometer using a slight modification of the method of Mason and Likar.[10] Unipolar and bipolar limb and three precordial leads (V_4, V_5 and V_6) were continuously monitored on an oscilloscope and recorded on a three channel direct ink-jet recorder with an amplitude calibration of 1 mv/cm (Mingograf 32, Elema-Schönander). After a 5 minute rest period, exercise was started at an initial work load of 200 kg-m/min, which was augmented every 4 minutes in increments of 200 kg-m/min until definite angina pectoris or exhaustion occurred. The appearance of S–T segment depressions or elevations was not sufficient reason to interrupt the test. Electrocardiographic recordings were made before and every minute during the actual exercise and during the immediate postexercise period until the heart rate and electrocardiographic abnormalities, if present, returned to preexercise values. The exercise electrocardiograms were read independently by two cardiologists. Only horizontal or downsloping S–T segment depressions were taken into account, and the degree of depression was expressed in millimeters. The exercise and postexercise periods were considered separately and the maximal ischemic S–T depression observed during each period was used in the study. The maximal heart rate reached during exercise was noted.

Atrial pacing test: This test was performed by means of a bipolar pacing catheter introduced into a right antecubital vein and advanced to the junction of the superior vena cava and right atrium. After a 5 to 10 minute period of rest, atrial pacing was started at a rate 10 beats above the control level, using the minimal voltage to assure stable pacing (Electrodyne TR-3). Every minute the heart rate was increased by 10 beats until definite angina pectoris or atrioventricular dissociation occurred. A 12 lead electrocardiogram was recorded on an eight channel ink-jet recorder (Mingograf 81, Elema-Schönander) just before, every minute during and for 5 minutes after pacing. Fifteen minutes later the test was repeated. If atrioventricular dissociation occurred at a rate lower than 140 beats/min during the first test, 1 mg of atropine sulfate was injected intravenously before the second test. The patient was not informed of the beginning or end of the pacing and was asked to inform the physician as soon as chest pain occurred and to describe its characteristics as accurately as possible. S–T segment depressions, occurring during pacing, were evaluated as described for the graded exercise test, at the maximal obtained heart rate.

Selective coronary arteriography: This procedure was performed in multiple projections according to the Sones technique.[11] A 6 inch Siemens image intensifier was linked with a cine-pulse unit. Recordings were made with an Arriflex camera at a rate of 40 frames/sec.

Coronary arterial lesions were classified on the basis of the severest narrowing in any of the following branches: dominant right coronary artery, left main trunk, anterior

descending, major diagonal branches, circumflex and major lateral or posterolateral branches. Patients with at least an estimated 75 percent narrowing of one of these branches were considered to have a positive coronary angiogram. On the basis of this angiographic criterion, patients were classified into two groups: those with severe coronary artery disease (group I) and those with a normal coronary angiogram or minor lesions (group II). The classification in each case was performed on two occasions, several months apart, by an experienced observer who had no knowledge of the patients' history or test results. The two interpretations were concordant except for those of one angiogram, which was analyzed by two other observers with concordant interpretations.

Statistical methods: Mean values ± 1 standard deviation are given. The *t* test was used for comparisons of height, weight, age, maximal obtained heart rate and serum cholesterol in both groups.

The diagnostic performance of the tests was judged in terms of sensitivity ($n_1/n_2 \times 100$) and specificity ($n_3/n_4 \times 100$):

n_1 = number of cases with a true positive test (either true positive clinical history or true positive stress electrocardiogram).

n_2 = total number of cases with a positive coronary angiogram.

n_3 = number of cases with a true negative test (either true negative clinical history or true negative stress electrocardiogram).

n_4 = total number of cases with a negative coronary angiogram.

Discriminant function analysis (stepwise method) was used to assess the independent diagnostic contribution of various parameters.

Results

Coronary angiogram: Group I comprised 40 patients with at least one severely stenotic artery. In 4 patients a single, in 32 patients two and in 4 patients three severe stenoses were present. Group II comprised 30 patients, 25 with a completely normal coronary angiogram, 3 with some irregularities of the vessel wall and 2 with less than 75 percent stenosis.

Clinical and laboratory findings: In 36 of 42 patients with a typical history of angina pectoris a positive coronary angiogram was found. A negative angiogram was found in 24 of 28 patients with "atypical chest pain." The sensitivity of the clinical history was 90 percent and its specificity 80 percent. Mean height, mean weight, mean age and mean systolic and diastolic blood pressures were similar in both groups. Three of the 11 female patients were classified in group I and 8 in group II.

A higher mean value for serum cholesterol was present in group I than in group II (264 ± 60.0 versus 227 ± 49.7 mg/100 ml) ($P < 0.01$).

S–T segment changes during and after graded exercise test (Table I): During exercise, ischemic S–T segment depression equal to or greater than 1 mm was observed in 24 patients in group I and in 3 patients of group II. Two of these three patients had a normal angiogram and one had less than 50 percent stenosis of both the right and left circumflex coronary arteries. With use of the same criterion, a negative tracing during exercise became positive during the postexercise period in two patients of group I and two patients of group II. The two latter patients had a normal angiogram.

TABLE II

Electrocardiographic Response to Exercise Testing and Atrial Pacing

Exercise	Atrial pacing	Number of Patients	
		Group I*	Group II†
+	+	24	5
+	−	2	0
−	+	5	4
−	−	9	21

* Group I = severe coronary artery disease determined angiographically.

† Group II = normal coronary arteries or minor lesions.

+ and − = respectively, greater than or equal to and less than 1 mm ischemic S–T segment depression, provoked by exercise or atrial pacing.

For ischemic S–T segment depression greater than or equal to 1 mm, the sensitivity of the graded exercise test was 65 percent and its specificity 83 percent. For ischemic S–T segment depression greater than or equal to 0.5 mm, 28 patients of group I and 10 patients of group II had a positive test during or after exercise. The calculated sensitivity and specificity of this criterion were, respectively, 70 and 66 percent. In the patients with positive responses, the maximal S–T segment depression was invariably recorded in the precordial leads V_4, V_5 and V_6.

Mean maximal heart rate during exercise was lower in group I than in group II (135 ± 24 versus 155 ± 21 beats/min) ($P < 0.001$).

S–T segment changes during atrial pacing test (Table I): Twenty-nine patients of group I and nine of group II manifested ischemic S–T segment depression equal to or greater than 1 mm during pacing. The sensitivity for this criterion was 72 percent and its specificity 70 percent. For an ischemic S–T segment depression equal to or greater than 0.5 mm, the sensitivity remained unchanged, but the specificity decreased to 63 percent. Mean maximal pacing rate was not significantly different in groups I and II (152 ± 20 versus 161 ± 20). Mean maximal pacing rate in the nine patients of group II with an ischemic S–T depression equal to or greater than 1 mm was 160 beats/min.

Comparison of exercise testing and atrial pacing for ischemic S–T segment depressions: For an ischemic S–T segment depression greater than or equal to 1 mm, 24 patients of group I and 5 patients of group II had both a positive exercise and pacing test (Table II). Both tests were negative in 9 patients of group I and 21 patients of group II. In seven patients of group I and four of group II, the test results were discordant. Of the four patients whose electro-

TABLE III

Correlation Between Clinical History, Electrocardiographic Response to Stress and the Presence or Absence of Severe Coronary Artery Disease

	Graded Exercise Test		Atrial Pacing	
	Group I*	Group II†	Group I*†	Group II†
Angina pectoris + ischemic S–T depression ⩾ 1mm	24	1	27	1
Angina pectoris + ischemic S–T depression <1 mm	12	5	9	5
No angina pectoris + ischemic S–T depression ⩾1 mm	2	4	2	8
No angina pectoris + ischemic S–T depression <1 mm	2	20	2	16

* Group I = severe coronary artery disease determined angiographically.

† Group II = normal coronary arteries or minor lesions.

cardiograms remained normal during the exercise test but became positive during the postexercise period, all but one patient (from group I) also had a positive response to atrial pacing.

Combination of clinical and electrocardiographic data: Clinical history and ischemic S–T segment depressions provoked by exercise and atrial pacing were correlated with the presence or absence of severe coronary artery disease on coronary angiograms (Table III). The combination of a typical history of angina pectoris with a positive electrocardiographic response to exercise or atrial pacing occurred in 25 and 28 patients, respectively. Only one of these patients had a normal angiogram. When atypical chest pain was accompanied by a normal electrocardiographic response to exercise or atrial pacing, the coronary vessels were normal in 91 and 88 percent, respectively, of the subjects. A discrepancy between clinical history and electrocardiographic response to exercise or atrial pacing occurred in one third of the cases.

The clinical and electrocardiographic responses to exercise and atrial pacing were correlated with the presence or absence of severe coronary artery disease (Table IV). The graded exercise and atrial pacing tests induced typical angina pectoris combined with a positive electrocardiographic response in 22 and 26 patients, respectively. All had severe coronary artery disease except one patient, whose clinical history was judged atypical. When a negative clinical and electrocardiographic response to exercise or atrial pacing occurred, the coronary vessels were normal in more than two thirds of the subjects.

Clinical response to exercise testing and atrial pacing in patients with a typical history of angina pectoris: The 42 patients with a typical history of angina pectoris are classified in Table V. Angina pectoris could be reproduced in 31 patients by exercise or atrial pacing, or both. All 31 manifested severe coronary artery disease on angiography. Angina pectoris could not be induced in the six patients with a history of angina pectoris and normal coronary arteries although their mean maximal heart rate was 147.5 ± 21.4 beats/min for the graded exercise test and 161.67 ± 7.5 for the atrial pacing test.

Exercise and atrial pacing did not induce angina pectoris in 10 and 8 patients, respectively, with severe coronary artery disease and a typical history of angina pectoris. The mean maximal heart rates obtained during exercise and pacing in these patients were, respectively, 140.6 ± 17 and 152.5 ± 28 beats/min.

Discriminant function analysis of factors contributing to the diagnosis of severe coronary artery disease: The following variables were used in the analysis: maximal ischemic S–T segment depression during exercise, maximal ischemic S–T segment depression after exercise, maximal heart rate during exercise, maximal ischemic S–T segment depression during atrial pacing, maximal obtained pacing rate and serum cholesterol values.

The final discriminant function equation revealed three significant ($P < 0.05$) factors:

A. Maximal S–T depression during exercise, expressed in millimeters ($t = 3.88$)

TABLE IV

Correlation Between the Clinical* and Electrocardiographic Responses to Stress and the Presence or Absence of Severe Coronary Artery Disease

	Graded Exercise Test		Atrial Pacing	
	Group I†	Group II‡	Group I†	Group II‡
Angina pectoris + ischemic S–T depression ⩾1 mm	21	1	25	1
Angina pectoris + ischemic S–T depression ⩽1 mm	7	2	5	2
No angina pectoris + ischemic S–T depression ⩾1 mm	5	4	4	8
No angina pectoris + ischemic S–T depression ⩽1 mm	7	23	6	19

* Clinical indicates typical angina pectoris during exercise or atrial pacing tests.

† Group I = severe coronary artery disease determined angiographically.

‡ Group II = normal coronary arteries or minor lesions.

B. Maximal heart rate during exercise, expressed in beats per minute ($t = -4.45$)

C. Serum cholesterol, expressed in milligrams per 100 milliliters ($t = 2.21$).

The discriminant function equation for the significant factors was:

$$\text{Severe CAD (1.0)} = 1.085 + 0.125\,A - 0.00788\,B + 0.00189\,C$$
$$(R = 0.66;\ SEy = 0.38)$$

where CAD (1.0) = presence (1) or absence (0) of severe coronary artery disease, and y = the dependent variable, severe coronary artery disease.

The introduction as a dependent variable of N_1/N and $-N_2/N$ for presence and absence of severe coronary artery disease changed the constant from 1.085 to 0.531 but did not influence the other factors of the discriminant function. (N = total number of cases, N_1 = number of cases with severe coronary artery disease, and N_2 = number of cases without severe coronary disease.)

Discussion

The presence or absence of an estimated 75 percent coronary arterial stenosis on angiography delineated a first group of subjects with severe and extensive disease and a second group, whose large majority of patients had normal coronary arteries. No differences in age, weight, height and blood pressure were found between the groups. Since patients with previous myocardial infarction, definite electrocardiographic abnormalities at rest or cardiomegaly were excluded, the major difference between groups was the presence or absence of severe coronary artery disease as defined by angiography. More female patients were present in the group with normal findings (27 percent) than in the group with severe coronary artery disease (8 percent).

The presence of a typical history of angina pectoris without coronary artery disease has been discussed by others.[12,13] Our study included six patients with a typical history of angina pectoris in the absence of coronary or valvular lesions. The prevalence of 14 percent is comparable to the prevalence of 17 percent reported in other studies.[3,4,6] However, the two stress tests did not reproduce the typical symptoms in our patients and provoked a positive electrocardiographic response in only one. These findings suggest a bias introduced into the clinical history by the doctor or the patient.

In our selected group of patients, a typical history of angina pectoris was a more sensitive (90 percent) than specific (80 percent) predictor of severe coronary artery disease. But it is difficult to explain why angina pectoris could not be induced by exercise or atrial pacing in a significant number of patients with a typical history and severe coronary artery disease (Table IV). Insufficient cooperation of these patients does not appear to be a factor since the maximal heart rate obtained during exercise testing or atrial pacing in this group did not differ from that of the total group.

TABLE V

Clinical Response to Exercise Testing and Atrial Pacing in 42 Patients with a Typical Clinical History of Angina Pectoris

Exercise Testing	Atrial Pacing	Number of Patients: Group I*	Number of Patients: Group II†
+	+	23	0
+	−	3	0
−	+	5	0
−	−	5	6

* Group I = severe coronary artery disease determined angiographically.

† Group II = normal coronary arteries or minor lesions.

+ and − = respectively, presence or absence of typical angina pectoris provoked by exercise or atrial pacing.

All our patients with a typical history of angina pectoris, confirmed by a positive clinical response during stress, proved to have severe coronary artery disease but no conclusion could be made when this confirmation was lacking. The evaluation of ischemic S–T segment depressions during exercise in our patients resulted largely in a confirmation of the results reported by others. Sensitivity (65 percent) and specificity (83 percent) of an S–T segment depression greater than or equal to 1 mm are in good agreement with data from other studies[3–6] in which an estimated 50 percent stenosis was used as the criterion for a positive coronary angiogram. However, since in our study only two subjects with coronary artery disease had less than 75 percent stenosis, the use of a less severe criterion for a positive angiogram does not substantially influence the results.

In our study the sensitivity was increased slightly by using the criterion of S–T segment depression greater than or equal to 0.5 (70 versus 65 percent), but the specificity of the test decreased markedly (66 versus 83 percent). In other studies the use of this less severe criterion also resulted in a small increase in sensitivity, counteracted by a larger decrease in specificity.[3] Data obtained from use of the three precordial leads V_4, V_5 and V_6 alone contained all the diagnostic information provided by the exercise tests. This finding may be a result of the diffuse nature of the disease in the large majority of our patients.

Atrial pacing appears to be slightly more sensitive in provoking ischemic S–T segment depressions than the graded exercise test (72 versus 65 percent). Lau et al.[14] suggested that atrial pacing was more sensitive in provoking ischemic S–T segment depressions than the double Master two-step test in patients with angina pectoris. However, the greater sensitivity was counteracted in our study by a larger decrease in specificity (70 versus 83 percent). All patients with a

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false positive exercise test also had a false positive atrial pacing test. In other words, there were no patients with a normal coronary angiogram who had a positive exercise test who did not have a positive atrial pacing test as well. The difference between the tests is probably explained by the higher heart rates that could be obtained by pacing.

The clinical diagnosis combined with the electrocardiographic diagnosis was correlated with the presence or absence of severe coronary artery disease. Fewer false negative results were obtained when the clinical diagnosis was based on the initial history rather than on interpretation of the chest pain occurring during the stress tests. The combination of clinical history and stress electrocardiogram had a very high predictive value when the data were concordant. No definite conclusion was possible when the clinical diagnostic data and stress electrocardiogram were discordant, although a trend favored the clinical diagnosis. No major differences in predictive value were found whether the electrocardiographic diagnosis was based on exercise testing or on atrial pacing.

Conclusions: The discriminant function analysis indicated that the atrial pacing test does not contribute significantly to the diagnosis of severe coronary artery disease in patients submitted to a graded exercise test. It also appears that the maximal heart rate obtained during exercise negatively correlates with severe coronary artery disease and is the best predictor of its presence, a fact heretofore inadequately stressed. Although the final regression coefficient ($r = 0.66$, $P < 0.001$) was highly significant, it was not high enough to allow the use of the discriminant function equation as a predictor for the diagnosis in individual patients.

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Pulmonary Arterial Diastolic Pressure in Acute Myocardial Infarction

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Pulmonary arterial diastolic pressure has been shown to be a reliable estimate of left ventricular filling pressure. In 91 patients with acute myocardial infarction, the Swan-Ganz flow-directed catheter was used to measure pulmonary arterial diastolic pressure, which was correlated with clinical and radiographic estimates of left ventricular failure. The physical findings of a third sound gallop and rales were significantly correlated with the level of pulmonary arterial diastolic pressure. In the absence of either a third sound gallop or rales, the pulmonary arterial diastolic pressure was found to be increased in 47 percent of the patients. The presence of rales was a less sensitive determinant of left ventricular dysfunction than a third sound gallop alone or in association with rales. Radiographic findings of increasing pulmonary congestion were significantly correlated with the level of pulmonary arterial diastolic pressure. In the absence of radiographic pulmonary congestion, 24 percent of patients had abnormal pulmonary arterial diastolic pressure. We conclude that measurement of pulmonary arterial diastolic pressure increases the objectivity of the clinical evaluation in patients with acute myocardial infarction.

In this era of coronary care units, myocardial failure is the most important factor determining hospital survival.[1] Evidence of heart failure on physical and radiographic examination is present in 40 to 50 percent of patients on admission to a coronary care unit, and the incidence reaches approximately 60 percent during the first 24 to 48 hours.[1–6] Previous studies from our laboratory[6] have revealed that a wide spectrum of hemodynamic changes is seen in patients with acute infarction studied early in their hospital course. The development of the balloon-tipped flow directed catheter by Swan and Ganz has introduced a rapid, safe and effective method for the measurement of right-sided cardiac pressures.[7]

The primary purpose of this study was to evaluate prospectively the correlation between pulmonary arterial diastolic pressure and several noninvasive clinical estimates of myocardial failure. The validity of the current system of subgrouping according to physical findings was investigated and a new radiographic classification is proposed.

Method

Ninety-one patients with acute myocardial infarction were studied. No patient had evidence of significant lung disease or mitral valve disease. The diagnosis of acute infarction was based on the following criteria: (1) a typical clinical history, and/or (2) electrocardiographic changes consisting of new Q waves or typical evolutionary ST–T changes, and (3) characteristic serial changes of serum enzymes including creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH). The patients were studied in the catheterization laboratory in the Myocardial Infarction Research Unit. A no. 5 or no. 7 Swan-Ganz catheter was inserted into

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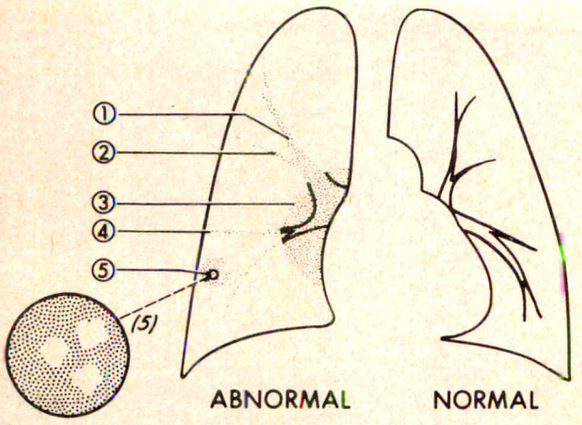

① *Cephalization*
② *Vascular Blurring*
③ *Hilar Haze*
④ *Outer Zone Vessels*
⑤ *Rossete Formation*

FIGURE 1. Schematic representation of the five radiographic signs used in evaluating left ventricular failure **(left)** and normal findings **(right).** Four radiographic grades were defined using these five signs: grade I, the absence of all parameters; grade II, cephalization and vascular blurring; grade III, cephalization, vascular blurring and hilar haze or outer zone vessels, or both; and grade IV, all five variables.

an antecubital vein, either percutaneously or by cutdown procedure, and advanced into the right atrium. In the right atrium, the balloon was inflated and the catheter advanced into the pulmonary artery. A no. 16 or no. 18 Teflon® needle was placed in the radial or brachial artery. Pressures were measured using a zero reference point 10 cm above the surface of the catheterization table or bed. The pressures were measured with a Hewlett-Packard transducer (no. 1280C) and recorded on a Hewlett-Packard multichannel oscillograph.

Clinical criteria for heart failure: One hour before the hemodynamic study, three observers evaluated the clinical status of the patient. On the basis of physical findings, patients were assigned to one of four classes. Class I was defined as no clinical evidence of congestive heart failure, that is, absence of a third sound gallop or rales, or both. Class II was defined as the presence of a third sound gallop or wet rales, or both. Patients in class III had overt pulmonary edema or pulmonary rales extending to above the midportion of the scapula. Patients in class IV had cardiogenic shock (systolic blood pressure less than 90 mm Hg, urinary output less than 20 cc/hour, peripheral vasoconstriction and an altered sensorium).[8] Patients in class II were further subgrouped into those with rales alone, a third sound gallop alone or both a third sound gallop and rales.

Radiographic criteria for heart failure: Radiographic evaluations were carried out within 1 hour of the hemodynamic study. Six-foot pulmonary arterial chest films were taken with the patient seated. Five standard criteria were used to characterize increasing degrees of pulmonary congestion[9,10]: (1) *cephalization,* defined as basilar pulmonary venous constriction with central and upper venous dilatation; (2) *pulmonary vascular blurring,* the lack of clarity of the margins of individual veins; (3) *hilar haze,* defined as blurring of the perihilar structures; (4) *outer zone vessels,* the visualization of venous vessels in the outer third of the lung fields; and (5) *rosette formation,* the presence of small clusters of radiolucent areas surrounded by a haze of water density (Fig. 1). Two radiologists independently evaluated each film to determine its radiographic grade. Four radiographic grades, using these five criteria, were determined: grade I, the absence of all variables; grade II, cephalization and vascular blurring; grade III, cephalization, vascular blurring and hilar haze or outer zone vessels, or both; and grade IV, the presence of all five variables.

Statistical evaluation: The data obtained were evaluated, using a general linear model program in which it was possible to do univariate analysis of variance on designs with one dependent variable and multivariate analysis of variance on designs with more than one variable. The multivariate procedure yielded multivariate tests of significance, enabling the user to select from either Hotalling's Trace Criterion, Roy's Largest Root Criterion, or Wilk's Statistics. In addition, univariate F- statistics for each of the dependent variables were provided. By appropriate blocking of the design matrix, the same program was also used to compare regression equations over several groups.[11]

Results

The 91 patients who underwent these hemodynamic studies were compared with 614 patients with a diagnosis of acute infarction, admitted to our Myocardial Infarction Research Unit during the past 6 years. No significant difference was found with respect to (1) age, (2) sex, (3) frequency of previous infarction, or (4) frequency of a previous history of heart failure. When the 91 patients were grouped according to clinical class, their hospital mortality rate was no different from that of patients of a similar class in the larger group of 614. However, the mortality rate in our study group was 34 percent, compared to an overall mortality rate of 22 percent in the group of 614. This finding reflects the higher percentage of patients in classes II, III and IV and the lower percentage of patients in class I in this study group than in our total series with documented infarction. Despite our efforts to study all patients with suspected infarction, there was obvious selection in favor of sicker patients. Thus, our series is not representative of all patients with infarction, although we believe that the hemodynamic findings in any given clinical class of patients are representative of the findings in other patients in a similar class.

Pulmonary arterial diastolic pressure and mortality rate: The patients studied ranged in age from 35 to 85 years (mean age 60.2 years); 73 percent were male. The mean time between admission and study was 12 hours, and 90 percent of the patients were studied less than 24 hours after the onset of symptoms. In the 29 patients in class I, the pulmonary arterial diastolic pressure was 13.8 ± 4.6 mm Hg. In this group, three patients died (hospital mortality rate 10 percent). There were 41 patients in class II who had a pulmonary arterial diastolic pressure of 20.3 ± 5.8 mm Hg, and the hospital mortality rate was 22 percent (9 patients). Four patients in class III had a pulmonary arterial diastolic pressure of 38.3 ± 8.7 mm Hg and three of the four died. The

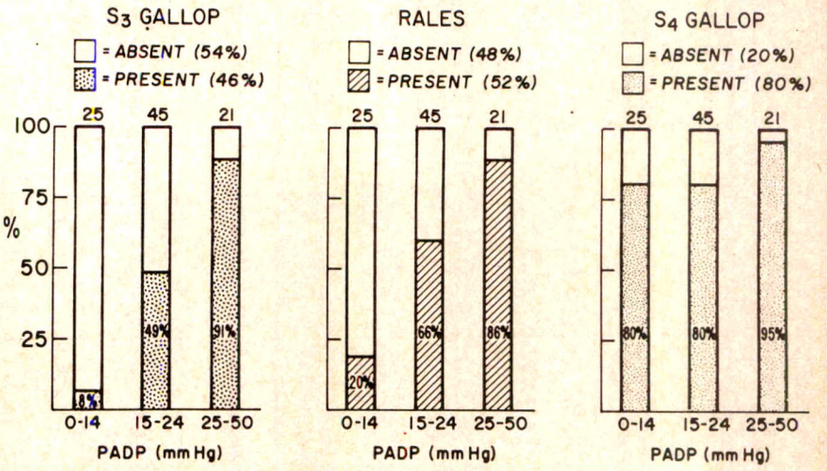

FIGURE 2. Relation of pulmonary arterial diastolic pressure (PADP) to the physical findings of third and fourth sound gallops and rales. The patients are classified into three categories on the basis of pulmonary arterial diastolic pressure. The number of patients in each pressure range is shown on top of the bar graphs. The percent of patients with the physical variable present, at each pressure range, is presented within the bar graphs.

pulmonary arterial diastolic pressure was 23.4 ± 9.5 mm Hg in 17 patients in class IV (hospital mortality rate 94 percent).

Correlation of pulmonary arterial diastolic pressure, third and fourth sound gallops, and rales: The relations of pulmonary arterial diastolic pressure to the physical findings of third and fourth sound gallops and rales are shown in Figure 2. The patients were classified in three categories on the basis of pulmonary arterial diastolic pressure: 0 to 14 mm Hg normal range; 15 to 24 mm Hg mild to moderate elevation; and 25 to 50 mm Hg severe elevation. A fourth sound gallop was noted in 80 percent of the patients and was found with equal frequency in all ranges of pulmonary arterial diastolic pressure. A third sound gallop was present in 46 percent (42 patients) of the total series. In these patients, the pulmonary arterial diastolic pressure was 24.4 ± 8.3 mm Hg compared to 15.1 ± 5.2 mm Hg in the 49 patients who had no third sound gallop. This difference was significant (P <0.001). Of 25 patients with a pulmonary arterial diastolic pressure of 14 mm Hg or less, only 2 (8 percent) had a third sound gallop. Of 21 patients with severely increased pulmonary arterial diastolic pressure, 18 (91 percent) had a third sound gallop. In the group with mild to moderate elevation, only 22 (49 percent) had a third sound gallop.

Rales were heard in 52 percent of the patients. The pulmonary arterial diastolic pressure in these 46 patients was 23.2 ± 9.1 mm Hg compared to 15.8 ± 5.4 mm Hg in the 45 patients without rales. This difference was significant (P <0.001). Five of the 25 patients (20 percent) with a normal pulmonary arterial diastolic pressure had rales, whereas 18 of the 21 patients (86 percent) with severe elevation had rales. In the group with mild to moderate elevation, rales were heard in 30 patients (66 percent). Thus, a third sound gallop and rales both correlated significantly with the level of pulmonary arterial diastolic pressure. However, although rales were heard in 20 percent of the patients with normal pulmonary arterial diastolic pressure, a third sound gallop was audible in only 8 percent of these patients.

The singular diagnostic value of the third sound gallop and pulmonary rales was further evaluated by substratification of patients (Fig. 3). In 34 patients without a third sound gallop or rales, the mean pulmonary arterial diastolic pressure was 15.2 ± 5.6 mm Hg; in 15 patients with rales but without a third sound gallop, this value was 16.5 ± 6.7 mm Hg. Eleven patients had a third sound gallop but no rales, and their pulmonary arterial diastolic pressure was 20.3 ± 6.2 mm Hg. In the 31 patients with both rales and a third sound gallop, the pressure was 25.8 ± 8.5 mm Hg. A significant difference (P <0.03) was found between the levels of pulmonary arterial diastolic pressure in patients with a third sound gallop (either alone or with rales) and those without a third sound gallop (with or without rales). No significant difference was noted between the group without rales or a third sound gallop and the group with rales only.

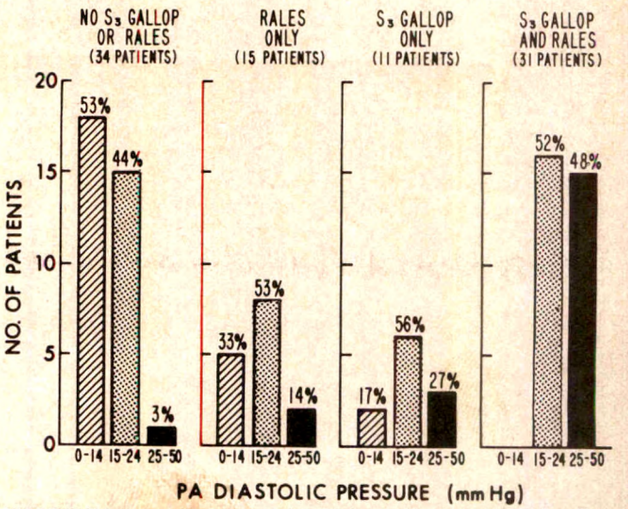

FIGURE 3. Diagnostic value of the third sound gallop and rales related to pulmonary arterial diastolic pressure. The number of patients at each pressure range in each subgroup is noted on the ordinate. The percent of the total group of patients within each subgroup at the three pressure ranges is presented above the bar graphs. PA = pulmonary arterial.

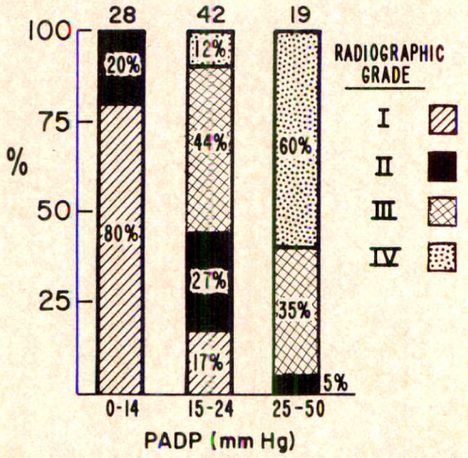

FIGURE 4. Pulmonary arterial diastolic pressure related to the radiographic evaluation. The number of patients within each pressure range is noted at the top of each bar graph. The percent of patients with the estimated radiographic grade within each pressure range is presented within the bar graphs.

Correlation of pulmonary arterial diastolic pressure and radiographic findings: The radiographic severity of pulmonary congestion and its relation to pulmonary arterial diastolic pressure is shown in Figure 4. This includes an evaluation of 88 technically satisfactory chest roentgenograms. Of 28 patients with a normal pulmonary arterial diastolic pressure, 80 percent had no radiographic evidence of pulmonary congestion. The remaining six patients in this group had all received a diuretic agent within 24 hours of study; the finding of a normal pulmonary arterial diastolic pressure but grade II X-ray changes in these patients may reflect the previously described lag between hemodynamic improvement and demonstration of radiographic improvement after therapy.[10] All 19 patients with severely increased pulmonary arterial diastolic pressure had radiographic evidence of pulmonary congestion and, in 18 of these, the radiographic grade was III or IV. Eighty-three percent of the patients with mild to moderate elevation of pulmonary arterial diastolic pressure had radiographic evidence of pulmonary congestion. Thus, of 59 patients with definite evidence of pulmonary congestion on X-ray film, 90 percent had an abnormal pulmonary arterial diastolic pressure. Of the 29 patients without radiographic evidence of pulmonary congestion, 76 percent had a normal pulmonary arterial diastolic pressure.

Discussion

Left ventricular filling pressure is a major determinant of ventricular performance through the well-known Frank-Starling relation.[12] Several studies of patients with acute myocardial infarction have revealed that right atrial pressure frequently does not reliably reflect changes of left ventricular filling pressure.[1,5,6,13,14] Thus, direct or indirect means of estimating left ventricular filling pressure are desirable. Although direct measurements of left ventricular pressure have been carried out, the need for arterial cannulation and the risk of ventricular irritability have made this procedure less than optimal.[5,15,16] At the end of diastole the left ventricle, left atrium and pulmonary vasculature form a functional conduit with only a small pressure gradient in the direction of flow.[17] Thus, in the absence of obstruction to pulmonary venous flow, a good correlation is expected between left ventricular filling pressure and pulmonary arterial diastolic or wedge pressures. In general, most studies have found a good correlation between pulmonary wedge and pulmonary arterial diastolic pressure and left ventricular end-diastolic pressure in patients with normal or only mildly abnormal left ventricular filling pressure.[17–20] However, a discrepancy in these two pressure measurements has been found with increasing degrees of left ventricular dysfunction.[17,20,21]

Correlation of pulmonary arterial diastolic pressure and clinical evidence of myocardial failure: The importance of the physical examination in patients with acute myocardial infarction has been previously emphasized.[22–24] An atrial (fourth sound) gallop is a frequent finding in the setting of acute myocardial infarction.[24,25] In our study it occurred frequently at all ranges of pulmonary arterial diastolic pressure and was not significantly related to this pressure. The presence of either a third sound gallop or rales has previously been considered an indication of left ventricular failure, and absence of both findings an indication of normal ventricular function.[8] In our patients with failure manifested by a third sound gallop or rales, or both, 85 percent had increased pulmonary arterial diastolic pressure. Furthermore, a significant difference in the pulmonary arterial diastolic pressure was noted when patients with a third sound gallop or rales were compared with patients who did not have these physical findings. Sjögren[2] found a similar significance when relating pulmonary arterial diastolic pressure to clinical rales and a third sound gallop. Hamosh and Cohn[5] measured left ventricular pressure directly and found a significantly higher level of end-diastolic pressure in patients with clinical evidence of failure than in those without failure.

Two important exceptions to the relation between a third sound gallop or rales and hemodynamic evidence of myocardial dysfunction were found in our study. Increased pulmonary arterial diastolic pressure was found in 47 percent of patients without clinical evidence of failure. The elevation of pulmonary arterial diastolic pressure or left ventricular filling pressure values in patients with acute infarction but no physical findings of failure has been noted previously.[1,5,16,26–29] Thus, although the presence of a third sound gallop and rales is highly significant and indicates increased filling pressure of the left ventricle, absence of these findings does not exclude the presence of left ventricular dysfunction in a large

number of cases. Furthermore, the presence of pulmonary rales in the absence of a third sound gallop was a less sensitive determinant of left ventricular dysfunction, manifested by increased pulmonary arterial diastolic pressure, than a third sound gallop alone or in association with rales. One third of the patients in the group with rales alone had a normal pulmonary arterial diastolic pressure.

Correlation of X-ray findings and signs of left ventricular failure: The conventional chest roentgenogram may provide one of the earliest signs of left ventricular failure. Derangements of left ventricular function lead to an increase in pulmonary venous pressure and the development of pulmonary venous hypertension.[9,10] Further degrees of left ventricular failure lead to added signs of interstitial edema including pulmonary venous blurring, hilar haziness, prominence of outer third venous markings and peri-acinar fluid transudation.[9,10,30] Harrison et al.[30] noted in their radiographic evaluation of patients with acute infarction that frequent radiographs were important for the early detection of left ventricular failure. Frequently, radiographic findings of congestion were noted before physical signs of cardiac failure. Our study demonstrated a significant correlation between increasing grades of pulmonary congestion on roentgenogram and increasing levels of pulmonary arterial diastolic pressure. More than 90 percent of patients with radiographic evidence of pulmonary congestion had abnormal pressure. All patients with grade III or IV radiographic changes had a pulmonary diastolic pressure greater than 15 mm Hg. Similar findings relating pulmonary arterial wedge pressure to radiographic signs of pulmonary congestion were noted by McHugh et al.[31] Sjögren[2] also reported a significant increase of pulmonary arterial diastolic pressure with increasing grades of pulmonary congestion. Hamosh and Cohn[5] found, in evaluating left ventricular end-diastolic pressure in acute infarction, that all patients with radiographic evidence of pulmonary congestion had pressures greater than 19 mm Hg. Discrepancies between the level of pulmonary arterial wedge pressure and the radiographic state of the lungs occurred in 10 percent of cases studied by McHugh et al.[31] These discrepancies were attributed to "preclinical failure," "post-therapeutic phase lag" or severe hypoxemia.[10,27] Our studies revealed some discrepancy in pulmonary arterial diastolic pressure in patients with normal radiographic findings. Twenty-four percent of patients without radiographic evidence of pulmonary congestion had increased pulmonary arterial diastolic pressure. Thus, like the third sound gallop, the presence of radiographic signs of pulmonary congestion correlates well with increased pulmonary arterial diastolic pressure but, like both a third sound gallop and rales, their absence does not exclude increased filling pressure.

In view of these findings of an abnormal level of pulmonary arterial diastolic pressure in the absence of clinical and radiographic evidence of left ventricular failure, it is important to recognize that increased left ventricular filling pressure does not necessarily signify left ventricular failure.[32,33] Previous studies[34] have revealed that serial changes in left ventricular size occur in many patients with acute infarction. In these patients an increase in end-diastolic volume and filling pressure is a reflection of impaired ventricular function and the use of the Frank-Starling mechanism to improve cardiac output.[35] Recent studies[32,36,37] have revealed in both the experimental animal and in man that reductions in left ventricular compliance are common in the setting of acute infarction. This decrease in compliance has been attributed to stiffening of the infarcted myocardium. In experimental studies of acute infarction, an increase in left ventricular end-diastolic pressure has been noted in the absence of an increase in end-diastolic volume and other findings of left ventricular failure.[36] The relative influence of an increase in end-diastolic volume and a change in compliance on the level of pulmonary arterial diastolic pressure in our patients cannot be determined from our study.

Clinical implications: It is clear from our study that hemodynamic measurements in the setting of acute myocardial infarction have improved understanding of the dynamics of infarction, and increased the objectivity of the clinical evaluations. Continuous monitoring of pulmonary arterial diastolic pressure can be useful in providing a clue to early hemodynamic derangements of the left ventricle.[29,38] With an increased understanding of left ventricular dysfunction, the proper interventions in this early state may prevent progressive deterioration. The measurement of pulmonary arterial diastolic pressure has been found useful in determining therapy, especially a need for volume expansion in some of the more severely ill patients, and has also proved important in the diagnosis of certain complications such as acute mitral insufficiency and ventricular septal rupture.[39,40] Much still needs to be learned about the hemodynamic effects of various agents, including digitalis and diuretic drugs, in the setting of acute myocardial infarction so that these agents can be used optimally.[2] The use of pulmonary arterial diastolic pressure as an index of left ventricular filling pressure will facilitate these studies.

The measurement of pulmonary arterial diastolic pressure thus has an important role in the daily management of patients with acute myocardial infarction and will provide a tool by which greater insight in the future management of patients will be possible. Our study has established the value of the pulmonary arterial diastolic pressure determination in one important capacity: improved understanding of the meaning of physical and radiographic findings.

Acknowledgment

We express our gratitude to Mrs. Laura Cook and Mr. Jack Goldman for their technical assistance. We also acknowledge the many helpful suggestions by Dr. Andrew G. Wallace.

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Early Sequential Changes in Left Ventricular Dimensions and Filling Pressure in Patients After Myocardial Infarction

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Early consecutive changes in pulmonary arterial end-diastolic pressure (PAEDP) and echocardiographic left ventricular dimensions were measured in 14 patients within the first 8 days after acute myocardial infarction. Left ventricular volumes were estimated from echocardiographic left ventricular dimensions. Left ventricular compliance was assessed by three formulas, $\Delta V/\Delta P$, $\Delta V/ESV/\Delta P$ and $LVID_d/PAEDP$, where ΔV = echocardiographic stroke volume, ΔP = a derived left ventricular diastolic pressure change from the lowest level of early diastolic to the end-diastolic pressure, ESV = left ventricular end-systolic volume, and $LVID_d$ = echocardiographic left ventricular end-diastolic dimension. To compare pressure, dimension and compliance values, linear relations were assumed between values for left ventricular end-diastolic volume, end-systolic volume, pulmonary arterial end-diastolic pressure and the day after infarction. The estimated third day values for the variables obtained from these linear relations were used so that each patient's values would contribute equal weight to the statistical analysis.

The estimated third day compliance values from each formula correlated highly with one another (r = 0.69–0.82). Neither $\Delta V/\Delta P$ nor $\Delta V/ESV/\Delta P$ had a significant correlation with $LVID_d$. Echocardiographic end-diastolic volume correlated with both end-systolic volume (r = 0.89) and echocardiographic stroke volume (r = 0.62) but not with pulmonary arterial end-diastolic pressure. When the first and last measurements for each patient are used, large changes in pulmonary arterial end-diastolic pressure associated with no or small alterations in echocardiographic left ventricular end-diastolic dimension in 12 patients imply acute changes in ventricular compliance. Sequential compliance values ($\Delta V/\Delta P$) increased in seven survivors and decreased in one. $\Delta V/\Delta P$ decreased in the five patients who died or had electrocardiographic evidence of extension of infarction. Early sequential changes in filling pressure, echocardiographic dimensions, and left ventricular compliance had a close correlation with the clinical course of the patients in our series and these data may assist in the management of patients with hemodynamic instability after acute myocardial infarction.

From the Division of Cardiology, Department of Medicine, University of Alabama Medical Center, Birmingham, Ala. This work was supported by the Myocardial Infarction Research Unit Program, Department of Health, Education and Welfare Contract PH 43-67-1441, and the Cardiovascular Research and Training Center, Department of Health, Education and Welfare Program Project Grant HE 11,310. Manuscript accepted July 11, 1973.

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Hemodynamic measurements made in patients soon after hospitalization for acute myocardial infarction have demonstrated various changes in left ventricular performance.[1–14] Several of these initial determinations have been useful in the early identification of patients with a poor prognosis. Among the measurements associated

with a high mortality rate are a pulmonary arterial end-diastolic pressure greater than 28 mm Hg, a combination of this pressure greater than 15 mm Hg and cardiac index less than 2.3 liters/min per m^2,[9] maximal value for the first derivative of left ventricular pressure (dP/dt) less than 1,000 mm Hg/sec,[2] left ventricular work less than 2.5 kg-m/min,[5] left ventricular stroke work index less than 25 g-m/beat per m^2,[10] and various indirect determinations of ventricular function made during isovolumic systole.[11–13] However, consecutive measurements of ventricular performance are required to identify progressive myocardial functional impairment in patients whose initial hemodynamic data do not indicate a poor prognosis.

An index of ventricular stiffness, which may be obtained for groups of patients, has been shown to be higher in patients studied 2 to 25 hours after acute myocardial infarction than in normal subjects or patients with coronary artery disease but no previous infarction.[14] Duplicate studies performed within a few days and 3 to 5 weeks after infarction have revealed that left ventricular end-diastolic pressure remains increased in many patients.[15,16] Increased left ventricular end-diastolic pressure and normal echocardiographic end-diastolic left ventricular internal dimension have been observed in five patients with clinical left ventricular failure within 24 hours after infarction.[16] The increased left ventricular end-diastolic pressure and normal echocardiographic internal dimensions persisted in the three patients studied 3 weeks after infarction. Increased left ventricular end-diastolic pressure and normal end-diastolic volume have been reported 4 and 8 weeks, respectively, after experimental myocardial infarction.[17] Thus, the decreased ventricular compliance measured within the first few hours of infarction appears to persist through the healing phase of the infarction. However, the relation between early sequential changes in left ventricular filling pressures, dimensions and compliance during the first few days after acute myocardial infarction in man have not been investigated. The purpose of the present study was to examine these relations and to determine their clinical significance.

Methods

Selection of Patients and Procedures

Fourteen patients, admitted to the Myocardial Infarction Research Unit (MIRU) of the University of Alabama Hospital because of severe chest pain, were studied by consecutive daily echocardiograms and simultaneous pulmonary arterial pressure recordings. The diagnosis of acute myocardial infarction was documented by the development of Q or QS waves on the electrocardiogram and characteristic serial serum enzyme changes. The nature and risks of the investigation were explained to the patient and a responsible family member, and informed consent was obtained in accordance with the Declaration of Helsinki.[18]

The patients ranged in age from 31 to 79 years (mean 54 years); 10 were male and 4 were female. The location of the infarct, as demonstrated by electrocardiogram, was anterior in three patients (Cases 4, 10 and 13, Table I), inferior in five (Cases 3, 5, 9, 11 and 12), anterolateral in three (Cases 1, 7 and 14), anteroseptal in one (Case 2) and inferolateral in one (Case 6). Patient 7 had a left bundle branch block pattern. Twelve patients (Cases 1 to 3, 5, 6 and 8 to 14) were studied because of systemic hypotension, one patient because of pulmonary edema (Case 7) and one for an extensive precordial impulse and a loud third sound gallop (Case 4). Four patients (Cases 4, 5, 9 and 12) had experienced a previous myocardial infarction. Seven patients gave a history of hypertension (Cases 1, 7, 9 to 12 and 14). Of six patients (Cases 1, 2, 7, 8, 12 and 14) who described symptoms of congestive heart failure, four (Cases 1, 7, 12 and 14) also had hypertension and one (Case 12) had had a previous myocardial infarction. A third sound gallop was heard in nine patients (Cases 1, 2, 4, 6, 8, 10 and 12 to 14). A fourth sound gallop was heard in 11 patients (Cases 1 to 4, 6, 7, 9 to 12 and 14) and third and fourth sound gallops were audible in 7 patients (Cases 1, 2, 4, 6, 10, 12 and 14).

Pulmonary arterial pressure was measured using a no. 7 Swan-Ganz catheter,[19] a P23D strain gauge and an 1800 IBM computer programmed to select the median pressure contour from a 9 second sample of consecutive contours. The procedure for continuous pressure monitoring has been described in detail previously.[1,7] Zero pressure reference was taken as 10 cm above the patient's back.

Echocardiograms were obtained at approximately the same time of day in each patient using a Smith-Kline Ekoline-20 Ultrasonoscope with 2.25 megaHz transducers "focused" at 5 or 10 cm. For analysis of left ventricular dimensions, the transducer was placed in the fourth left intercostal space and directed posteriorly and laterally to resolve clearly the interventricular septum and left ventricular free wall endocardium and epicardium simultaneously. Echoes from the posterior leaflet of the mitral valve were recorded anterior to the left ventricular endocardium so that the position in the left ventricle at which consecutive dimensions were measured was essentially the same for each patient (position two as designated by Feigenbaum[20]). Echocardiographic left ventricular volumes were estimated as the cube of the end-diastolic ($LVID_d$) and end-systolic ($LVID_s$) internal left ventricular dimensions assuming a prolate ellipsoid reference figure for the left ventricle and a major to minor axis ratio of 2:1.[21] The echocardiographic $LVID_d$ was measured as the vertical distance in centimeters between the left ventricular side of the interventricular septum and the left ventricular endocardium at the time of the R wave of a simultaneously recorded electrocardiogram. The $LVID_s$ was measured as the shortest vertical distance between interventricular septum and left ventricular endocardium during systole.[20]

Evaluation of Left Ventricular Compliance

Left ventricular compliance was assessed by three formulas:

$$\Delta V/\Delta P \quad (1)$$

$$(\Delta V/ESV)/\Delta P \quad (2)$$

$$LVID_d/PAEDP \quad (3)$$

where ΔV = the diastolic volume change in milliliters or the end-diastolic volume (EDV) minus the end-systolic volume (ESV), both volumes calculated from echocardiographic dimensions of the left ventricle; ΔP = the left ventricular diastolic pressure change, in millimeters of mercury, which was estimated from the pulmonary arterial end-diastolic pressure; ESV = the end-systolic volume, in mil-

TABLE I

Echocardiographic Left Ventricular Dimensions and Volumes, Pulmonary Arterial End-Diastolic Pressures, Derived Left Ventricular Diastolic Pressure Changes and Compliance Values in 14 Postinfarction Patients

		Echocardiographic Estimates					Pressure Measurements (mm Hg)			Ratios		
											ΔV/ESV	$LVID_d$
Case no.	Day After Infarction	$LVID_d$ (cm)	$LVID_s$ (cm)	EDV (ml)	ESV (ml)	SV or Diastolic ΔV (ml)	PAEDP	Est. LVEDP	ΔP	ΔV/ΔP (ml/mm Hg)	ΔP ($mm\ Hg^{-1}$)	PAEDP (cm/mm Hg)
1	0	6.90	6.30	329	250	79	38	37.0	24.6	3.22	0.013	0.182
	1	5.55	4.85	171	114	57	17	20.6	14.7	3.87	0.034	0.327
	5	6.10	5.20	227	141	86	19	22.2	15.7	5.10	0.037	0.317
2	1	5.15	4.00	137	64	73	22	24.5	17.1	4.27	0.067	0.234
	2	5.20	4.20	141	74	67	23	25.3	17.5	3.82	0.051	0.226
	3	4.55	3.70	94	51	43	22	24.5	17.1	2.51	0.049	0.206
	6	4.80	3.70	111	51	60	24	26.1	18.0	3.33	0.065	0.200
	7	4.50	3.85	91	57	34	21	23.7	16.6	2.04	0.036	0.214
	8	4.15	3.30	71	36	35	24	26.1	18.0	1.94	0.054	0.174
3	5	6.00	5.00	216	125	91	12	16.7	12.4	7.34	0.059	0.500
	6	5.75	4.70	190	104	86	7	12.8	10.1	8.54	0.082	0.821
4	0	5.00	3.00	125	27	98	21	23.7	16.6	5.90	0.218	0.238
	1	5.25	3.70	145	51	94	12	16.7	12.4	7.58	0.149	0.438
5	0	4.31	3.10	80	30	50	12	16.7	12.4	4.03	0.134	0.359
	1	4.70	3.45	104	41	63	22	24.5	17.1	3.69	0.090	0.213
6	2	4.10	3.10	69	30	39	19	22.2	15.7	2.49	0.083	0.216
	3	5.05	4.15	129	71	58	19	22.2	15.7	3.70	0.052	0.266
7	1	5.50	3.95	166	62	104	20	22.9	16.1	6.44	0.103	0.275
	2	5.55	3.85	171	57	114	16	19.8	14.3	7.99	0.140	0.347
8	3	6.00	5.00	216	125	91	29	30.0	20.3	4.47	0.036	0.207
	4	6.05	5.10	221	133	88	27	28.4	19.4	4.28	0.032	0.222
	5	6.25	5.50	244	166	78	31	31.5	21.3	3.67	0.022	0.201
9	2	4.65	3.95	101	62	39	13	17.5	12.9	3.03	0.049	0.358
	3	4.70	3.50	104	43	61	14	18.3	13.3	4.57	0.106	0.336
	4	4.75	3.55	107	45	62	8	13.6	10.5	5.89	0.131	0.593
10	0	4.80	3.70	111	51	60	21	23.7	16.6	3.61	0.071	0.229
	1	4.70	3.85	104	57	47	23	25.3	17.5	2.67	0.047	0.204
	2	4.85	4.05	114	66	48	25	26.8	18.5	2.60	0.039	0.194
11	1	5.05	4.35	129	82	47	21	23.7	16.6	2.83	0.035	0.240
	2	4.70	3.30	104	36	68	17	20.6	14.7	4.61	0.128	0.276
	3	5.00	4.00	125	64	61	19	22.2	15.7	3.89	0.061	0.263
12	0	4.25	3.00	77	27	50	5	11.2	9.1	5.47	0.203	0.851
	1	4.75	3.55	107	45	62	16	19.8	14.3	4.34	0.097	0.297
	2	4.55	3.70	94	51	43	14	18.3	13.3	3.22	0.063	0.325
13	1	5.10	3.80	133	55	78	13	17.5	12.9	6.06	0.110	0.393
	2	5.00	3.20	125	33	92	24	26.1	18.0	5.10	0.155	0.208
	3	5.10	3.30	133	36	97	24	26.1	18.0	5.38	0.150	0.212
	4	5.30	3.50	149	43	106	36	35.4	23.6	4.49	0.104	0.147
14	1	5.30	4.40	149	85	64	23	25.3	17.5	3.64	0.043	0.230
	2	5.10	4.00	133	64	69	19	22.2	15.7	4.40	0.069	0.269
	3	5.15	3.95	137	62	75	14	18.3	13.3	5.17	0.081	0.365

ΔP = left ventricular diastolic pressure change, estimated from pulmonary arterial end-diastolic pressure; ΔV = diastolic volume change or end-diastolic volume minus end-systolic volume, calculated from echocardiographic dimensions of the left ventricle; ΔV/ESV = fractional diastolic volume change; EDV = end-diastolic volume; Est. = estimated; ESV = end-systolic volume; LVEDP = left ventricular end-diastolic pressure; $LVID_d$ = echocardiographic left ventricular end-diastolic internal dimensions; $LVID_s$, = echocardiographic left ventricular end-systolic internal dimensions; PAEDP = pulmonary arterial end-diastolic pressure; SV = stroke volume.

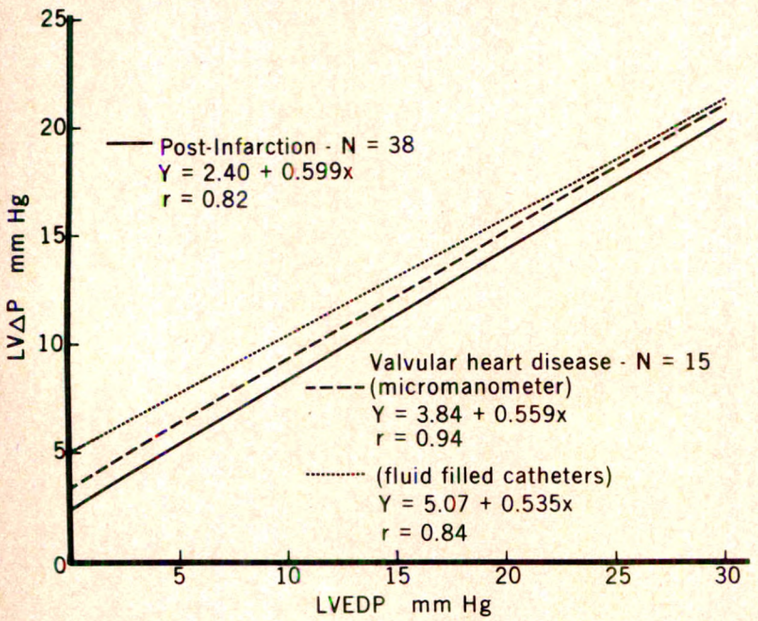

FIGURE 1. Regression lines for the relation between change in left ventricular diastolic pressure (LVΔP) and left ventricular end-diastolic pressure (LVEDP) for 38 patients with ischemic heart disease and 15 patients with valvular heart disease.

liliters, calculated as echocardiographic $(LVID_s)^3$; ΔV/ESV = the fractional diastolic volume change; $LVID_d$ = the echocardiographic left ventricular end-diastolic internal dimensions, in centimeters; PAEDP = pulmonary arterial end-diastolic pressure, in millimeters of mercury.

Two assumptions were required for the estimation of left ventricular diastolic pressure change (LVΔP) from the pulmonary arterial end-diastolic pressure. First is that LVΔP has a significant relation with left ventricular end-diastolic pressure (LVEDP). In 38 postinfarction patients studied previously in our laboratory, diastolic LVΔP had a significant linear correlation with LVEDP ($r = 0.82$; $P = 6.0 \times 10^{-7}$). The regression line between diastolic LVΔP and LVEDP for the 38 postinfarction patients illustrated in Figure 1 compares very favorably with regression lines from 15 patients with valvular heart disease whose left ventricular pressures were measured by both micromanometer and fluid-filled catheters in our laboratory. The formula relating diastolic LVΔP and LVEDP for the postinfarction patients is: LVΔP = 2.40 + 0.599 (LVEDP).

The second assumption is that the pulmonary arterial end-diastolic pressure is a reasonable estimate of the left ventricular end-diastolic pressure. For 95 observations made in 12 patients studied independently in the Myocardial Infarction Research Unit after acute myocardial infarction, PAEDP correlated linearly with simultaneous or contiguous LVEDP ($r = 0.86$ and $P < 0.001$ for PAEDP values ranging from 10 to 50 mm Hg).[22] The formula relating LVEDP to PAEDP is LVEDP = 7.34 + 0.78 (PAEDP). Since simultaneous left ventricular and pulmonary arterial pressures were not obtained in these patients, no direct correlation between PAEDP and diastolic LVΔP was possible. Therefore, diastolic LVΔP was estimated from PAEDP using the previously described relations.

Data Analysis

To examine the relations between early changes in left ventricular dimensions, filling pressures and compliance, the data were processed to permit values for each patient to contribute equal weight to the statistical analysis. The 14 patients did not always undergo measurements on successive days and data collection was not always started on the day of onset of chest pain (day zero). A straight line was fitted to values for end-diastolic volume versus values for the day after onset of chest pain for each patient. A similar linear relation was used for echocardiographic end-systolic volume and for pulmonary arterial end-diastolic pressure values versus day after the onset of chest pain since the data did not contradict the assumption of linear daily trends for these variables. For comparison of pressure and left ventricular dimension and compliance variables, estimated values for the third day after onset of chest pain were selected since most patients underwent measurements on or close to this day.

The slopes and intercepts of the relations between end-diastolic volume, end-systolic volume, pulmonary arterial end-diastolic pressure and the day after the onset of chest pain were used to obtain an equation by multiple regression analysis that would predict death or extension of the infarction. Multiple regression analysis was performed using the slopes and intercepts as independent variables and extension of the infarction or death as the dependent variable. A regression equation was calculated from the data using values for the dependent variable of zero for survival without electrocardiographic evidence of extension of infarction and one for extension of infarction or death. Extension of infarction occurred in 2 patients who survived (Case 10 and 13) and was defined as the development of elevated S–T segments and, subsequently, Q waves or persistent loss of R wave voltage in electrocardiographic leads other than those that demonstrated abnormalities upon admission. Evidence of extension of infarction occurred on day 2 in both patients.

Results

Values for echocardiographic left ventricular dimensions, filling pressures, ventricular volumes, estimated ΔP, and compliance indexes for the 14 postinfarction patients are presented in Table I. In Table II the slope and intercept values of the linear relations

TABLE II

Intercept (I) and Slope (S) Values for the Linear Relations Between Echocardiographic End-Diastolic Volume (EDV), End-Systolic Volume (ESV), Pulmonary Arterial End-Diastolic Pressure (PAEDP) and Day After Onset of Chest Pain

Case no.	I_{EDV} (ml)	S_{EDV} (ml/day)	I_{ESV} (ml)	S_{ESV} (ml/day)	I_{PAEDP} (mm Hg)	S_{PAEDP} (mm Hg/day)
1	246.9	−8.3	174.1	−9.1	29.9	−2.6
2	143.3	−8.0	70.7	−3.4	22.1	0.1
3	346.0	−26.0	230.0	−21.0	37.0	−5.0
4	125.0	20.0	27.0	24.0	21.0	−9.0
5	80.0	24.0	30.0	11.0	12.0	10.0
6	−51.0	60.0	−52.0	41.0	19.0	0.0
7	161.0	5.0	67.0	−5.0	24.0	−4.0
8	179.3	11.7	112.2	8.3	25.0	1.0
9	88.3	5.4	56.3	−1.3	19.2	−2.5
10	108.2	1.5	50.5	7.5	21.0	2.0
11	123.3	−2.0	78.7	−9.0	21.0	−1.0
12	84.2	8.5	29.0	12.0	7.2	4.5
13	121.0	5.6	50.0	−3.3	7.0	6.9
14	154.3	−8.0	92.0	−10.5	27.7	−4.5

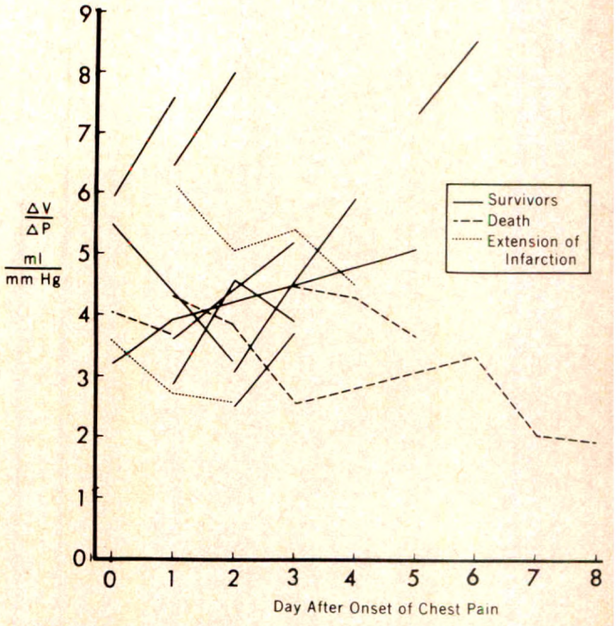

FIGURE 2. Early sequential changes in compliance after acute myocardial infarction. $\Delta V/\Delta P$ = echocardiographic stroke volume divided by left ventricular diastolic pressure.

between end-diastolic volume (EDV), end-systolic volume (ESV), and pulmonary arterial end-diastolic pressure (PAEDP) and day after infarction are displayed for each patient. The estimated third day values for the volume, pressure and compliance variables were determined from these relations.

Correlation of left ventricular volume, pressure and compliance variables: Utilizing the estimated third day values for all 14 patients, the three compliance indexes had significant direct linear correlations with each other. $\Delta V/\Delta P$ correlated with $\Delta V/ESV/\Delta P$ ($r = 0.869$; $P = 2.5 \times 10^{-4}$) and with $LVID_d/PAEDP$ ($r = 0.820$; $P = 8.6 \times 10^{-4}$), and $\Delta V/ESV/\Delta P$ correlated with $LVID_d/PAEDP$ ($r = 0.689$; $P = 0.009$). Neither $\Delta V/\Delta P$ nor $\Delta V/ESV/\Delta P$ had significant correlations with $LVID_d$. Correlations between single volume and pressure variables revealed that end-diastolic volume had a very significant direct linear relation with end-systolic volume ($r = 0.886$; $P = 9 \times 10^{-5}$), a reduced direct linear relation with stroke volume ($r = 0.617$; $P = 0.018$) and no significant correlation with pulmonary arterial end-diastolic pressure. The latter variable had no significant correlation with either end-systolic volume or stroke volume.

Figure 2 presents left ventricular compliance measured as $\Delta V/\Delta P$ versus day after the onset of chest pain. The lower limit of normal for $\Delta V/\Delta P$ obtained from nine normal subjects studied in our laboratory was 8.0 ml/mm Hg.[23] An increase in $\Delta V/\Delta P$ above initial values was associated with survival in eight patients. A decrease in $\Delta V/\Delta P$ from relatively low initial values was associated with either electrocardiographic evidence of extension of the infarction (two patients) or death (three patients). One survivor, who demonstrated a reduction in $\Delta V/\Delta P$ from an initial value of 5.5 ml/mm Hg, had an extensive precordial impulse on admission that diminished in size coincident with the decrease in compliance.

The relation between alterations in $LVID_d$, pulmonary arterial end-diastolic pressure and left ventricular compliance obtained with use of the first and last values for these variables is presented in Table III. Nine of the 14 patients showed less than 5 percent variation in $LVID_d$. Six of these demonstrated an average decrease in pulmonary arterial end-diastolic pressure of 32 percent and an increase in $\Delta V/\Delta P$ of 28 percent. Three had an average increase of 69 percent in pulmonary arterial end-diastolic pressure and a decrease of 31 percent in $\Delta V/\Delta P$. Five of the 14 patients had 5 to 20 percent changes in $LVID_d$ associated with much larger changes in $\Delta V/\Delta P$. There was no consistent relation between the directional changes for $LVID_d$ and $\Delta V/\Delta P$, nor was there a statistically significant correlation between the changes in $LVID_d$ and changes in $\Delta V/\Delta P$. In 12 of the 14 patients, alterations in $\Delta V/\Delta P$ were primarily related to changes in filling pressure.

Prediction of death or extension of infarction: The linear relations of end-diastolic volume, end-systolic volume and pulmonary arterial end-diastolic pressure versus values of the day after infarction were used to predict death or extension of the infarction. Using the intercepts of values for end-diastolic and end-systolic volume and the slope and intercept of pulmonary arterial end-diastolic pressure as independent variables and death or extension of the infarction as the dependent variable, multiple regres-

TABLE III

Relations Between Changes in Left Ventricular End-Diastolic Dimension, Pulmonary Arterial End-Diastolic Pressure and Compliance*

Changes in $LVID_d$	Changes in PAEDP	Changes in Compliance ($\Delta V/\Delta P$)	Number of Patients
<±5%	− (average 32%)	+ (average 28%)	6
	+ (average 69%)	− (average 31%)	3
+ 5 to 10%	+ (average 134%)	− (average 25%)	2
− 10 to 20%	− 50%	+ 37%	1
	+ 8%	− 77%	1
+10 to 20%	0	+ 33%	1

* Data based on first and last values for these variables in the 14 cases.

− = decrease; + = increase; ± = increase or decrease; 0 = no change.

$\Delta V/\Delta P$ = echocardiographic stroke volume divided by left ventricular end-diastolic pressure; $LVID_d$ = echocardiographic left ventricular end-diastolic internal dimensions; PAEDP = pulmonary arterial end-diastolic pressure.

sion analysis yielded a regression equation ($r^2 = 0.63$ and $P = 0.044$) that accurately predicted death or extension of the infarction in the 14 patients. The r^2 value represents the square of the multiple linear correlation coefficient and provides an estimate of the predictive power of the regression equation. The equation is:

$$y = -0.873 + 0.010(I_{EDV}) - 0.015(I_{ESV}) + 0.047(I_{PAEDP}) + 0.122\,(S_{PAEDP})$$

where: y = the predictive index; I_{EDV}, I_{ESV} and I_{PAEDP} = intercept values for end-diastolic volume, end-systolic volume and pulmonary arterial end-diastolic pressure; and S_{PAEDP} = the slope value of pulmonary arterial end-diastolic pressure (mm Hg/day). The average predictive index of patients who lived was 0.13 and that for patients who died or had extension of infarction was 0.76. In the group of 14 patients, every patient whose predictive index was less than the mid-point between these two averages (0.45) lived, and every patient with a value above 0.45 either died or had extension of infarction.

Discussion

The use of pulmonary arterial end-diastolic pressure to represent left ventricular filling pressure and echocardiographic left ventricular dimensions to estimate left ventricular volumes provides a convenient approximation of these variables in acutely ill patients. Pulmonary arterial end-diastolic pressure has been challenged[24,25] and supported[9,26] as an indicator of left ventricular end-diastolic pressure in patients with acute myocardial infarction. The use of pulmonary arterial end-diastolic pressure to estimate diastolic LVΔP assumes that the former adequately reflects left ventricular end-diastolic pressure and that there is a significant relation between the latter and diastolic LVΔP. These assumptions have been supported by data obtained from patients with ischemic and valvular heart disease. A direct correlation between pulmonary arterial end-diastolic pressure and diastolic LVΔP was not obtained in our group of postinfarction patients since simultaneous recordings of pulmonary arterial and left ventricular end-diastolic pressure were not available.

Although some workers[27] have described poor correlations between echocardiographic and single plane cineangiographic left ventricular volume values in patients with left ventricular asynergy, others[28] have demonstrated significant correlations when echocardiographic ventricular volumes are calibrated against more accurate biplane cineangiographic left ventricular volume determinations. In the latter study the correlation for end-diastolic volumes was slightly greater than that for end-systolic volumes, suggesting that regional abnormalities of myocardial contraction may have a greater effect on ultrasound estimates of end-systolic volume than on estimates of end-diastolic volume in the absence of marked distortion in the diastolic ventricular configuration due to aneurysm. Preservation of myocardial function at the base of the heart where echocardiographic dimensions are measured for volume determinations could result in a falsely low value for end-systolic volume, an overestimation of stroke volume (or diastolic ΔV) and, thus, less abnormal compliance values for the postinfarction patients. These errors may be less significant in comparing relative sequential changes in dimension and compliance in the same patient since the magnitude of the error probably would remain relatively constant for any particular patient during the first few days after infarction.

The substantially greater sequential changes in left ventricular filling pressure than in left ventricular dimensions in 12 of the 14 postinfarction patients imply shifts from one diastolic pressure-volume curve to another rather than changes in slope along the same curve. Under a particular set of circumstances, an intact ventricle operates along a certain segment of a longer diastolic pressure-volume curve which could be obtained from a wide range of diastolic pressure and volume measurements. Since this segment approaches linearity, its slope may be expressed by the formula $\Delta V/\Delta P$, as defined in this study, or its reciprocal ($\Delta P/\Delta V$), as used in previous investigations.[14] Changes in values for $\Delta V/\Delta P$ after myocardial infarction could result from alterations in ventricular volume alone or from changes in the physical characteristics of the ventricular wall. Since little change was observed in sequential left ventricular dimensions in our study, sequential changes in compliance may be attributed mainly to alterations in the physical properties of the ventricular wall.

Theoretically, the incorporation of fractional diastolic volume change ($\Delta V/ESV$) into the compliance formula would distinguish between two ventricles of different size with similar diastolic pressure-volume

slopes (that is, with the same $\Delta V/\Delta P$ value). However, since sequential changes in ventricular dimensions were small, the evaluation of sequential changes in compliance in a particular patient was not enhanced by calculating fractional diastolic volume change, as evidenced by the high correlation between $\Delta V/\Delta P$ and $\Delta V/ESV/\Delta P$ ($r = 0.87$; $P = 2.5 \times 10^{-4}$).

Prognostic value of sequential compliance measurements: The determination of $\Delta V/\Delta P$ from pulmonary arterial end-diastolic pressure and echocardiographic left ventricular dimensions requires several assumptions that have been discussed previously. The significant correlation between $\Delta V/\Delta P$ and the ratio of $LVID_d/PAEDP$ suggests that this ratio may provide a convenient guide to consecutive compliance changes in patients with acute myocardial infarction. The formulas $\Delta V/\Delta P$ and $LVID_d/PAEDP$ are not interchangeable since $\Delta V/\Delta P$ represents the slope of and $LVID_d/PAEDP$ denotes a point on the diastolic pressure-volume curve. Nevertheless, the direction and magnitude of change in these two variables were similar in our study. A decrease in left ventricular compliance during the first few days after acute myocardial infarction, as observed in patients who died or had electrocardiographic evidence of extension of infarction, appears to indicate a progressive increase in the amount of ischemic myocardium. An increase in compliance values in patients who survived suggests that some initially ischemic areas of left ventricle recovered within the first few days.

In addition to assessment of the prognostic value of sequential compliance measurements, a predictive equation was determined by multiple regression analysis of the slopes and intercepts of the linear relations of echocardiographic end-diastolic and end-systolic volumes and pulmonary arterial end-diastolic pressure versus day after infarction. In the small series described here, values from the predictive equation separated the patients who died or had extension of infarction from those who survived. Therefore, the monitoring of early trends in left ventricular dimensions and filling pressure may aid in the management of patients with hemodynamic instability after acute myocardial infarction.

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Left Ventricular A Wave Amplitude in Patients After Myocardial Infarction

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The relations between left ventricular (LV) A wave amplitude and left ventricular dimensions, compliance, systolic function, and the size of abnormally contracting segments (ACS) of the left ventricle were examined in 42 patients studied within 1 year after acute myocardial infarction. Left ventricular A wave amplitude was measured from left ventricular pressure tracings both from zero (A_0) and from pre-A wave pressures (A_{PAP}). Left ventricular compliance was calculated from left ventricular volumes obtained from biplane angiograms and the left ventricular pressure recorded immediately before angiograms. Left ventricular compliance was evaluated by three formulas: $\Delta V/\Delta P$ (angiographic stroke volume/left ventricular end-diastolic pressure (LVEDP) minus lowest early diastolic pressure); ΔV/LV end-systolic volume/ΔP; and $dV/dP_{ED} \times 1/EDV/m^2$. Percent ACS was measured as the akinetic or dyskinetic length along the end-diastolic perimeter on biplane left ventricular angiograms expressed as a percentage of the total left ventricular diastolic perimeter.

A_0 had a direct quadratic relation with A_{PAP} ($r^2 = 0.72$), and A_0 had high inverse quadratic correlations with $\Delta V/\Delta P$ ($r^2 = 0.59$), $\Delta V/ESV/\Delta P$ ($r^2 = 0.63$), and $dV/dP_{ED} \times 1/EDV/m^2$ ($r^2 = 0.72$). A_0 correlated directly with LVEDP ($r^2 = 0.76$), end-diastolic volume ($r^2 = 0.32$), LV mass ($r^2 = 0.22$) and percent ACS ($r^2 = 0.36$), and inversely with ejection fraction ($r^2 = 0.43$).

Seven of the 42 patients were studied by dextran infusion. Diastolic volume change ($\Delta V_{Ind.-Dil.}$) calculated from indicator-dilution cardiac output values, left ventricular diastolic pressure change (ΔP), and A_0 were obtained before infusion and after each 200 ml infusion. Values for diastolic pressure-volume slope ($\Delta P/\Delta V_{Ind.-Dil.}$) and A_0 increased with dextran infusion in all seven patients. The $\Delta P/\Delta V_{Ind.-Dil.}$ slopes had a significant direct linear relation with corresponding left ventricular A wave amplitudes. Thus, the slope of the diastolic pressure-volume curve for any ventricle, as reflected by the compliance values, is a major determinant of the increase in left ventricular A wave amplitude for a particular volume of dextran infused.

In summary, increased left ventricular A wave amplitudes in patients after myocardial infarction signify a decrease in both left ventricular diastolic compliance and systolic function.

From the Division of Cardiology, Department of Medicine, University of Alabama Medical Center, Birmingham, Ala. This work was supported by the Myocardial Infarction Research Unit Program, Department of Health, Education and Welfare Contract PH 43-67-1441 and the Cardiovascular Research and Training Center, Department of Health, Education and Welfare Program Project Grant HE 11,310. Manuscript accepted July 11, 1973.

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The A wave in left ventricular pressure records coincides with atrial systole, and increased A wave amplitudes have been observed in patients with aortic stenosis, aortic stenosis and insufficiency and ischemic heart disease.[1–4] These large A waves in left ventricular pressure tracings have been attributed to forceful left atrial contractions that elevate left ventricular end-diastolic pressure above the level of mean left atrial pressure and thus enhance left ventricular end-diastolic fiber stretch in ventricles with diminished diastolic distensibility.[1,3] In the absence of mitral stenosis the degree to which left ventricular

diastolic myocardial fiber stretch is augmented by atrial contraction is dependent upon the slope of the diastolic pressure-volume curve at the time of atrial systole and the force of atrial contraction.[1–6] Left atrial systole has been demonstrated to contribute an average of 29 percent of the left ventricular end-diastolic volume in patients with aortic stenosis, 27 percent in patients with ischemic heart disease and 21 to 26 percent in control subjects.[2,3]

Increased A wave amplitudes of apex cardiograms have been reported at rest, after exercise and during chest pain in many patients with ischemic heart disease.[7,8] An increase in A ratio (A wave amplitude divided by the maximal vertical excursion of the apex cardiogram) has been correlated with increased left ventricular end-diastolic pressure,[8,9] and prominent A waves in apex cardiograms have been associated with large A waves in simultaneously recorded left ventricular pressure tracings.[8–13] The magnitude of A waves in both left ventricular pressure tracings and apex cardiograms has been attributed to the left ventricular pressure before atrial contraction, left ventricular volume, left ventricular compliance and left atrial function.[1–7,9] It has been suggested that decreased left ventricular compliance or distensibility is a major determinant of the increased left ventricular A waves observed in patients with ischemic heart disease.[7,10,13–15] However, no quantitative study relating left ventricular A wave amplitude to left ventricular dimensions, diastolic pressure-volume relations and systolic performance has previously been performed in patients with ischemic heart disease. In this investigation the magnitude of A waves in left ventricular pressure tracings was related in a quantitative manner to left ventricular pressure, volume, compliance, systolic function and the extent of left ventricular segmental disease in patients studied within a year after acute myocardial infarction.

Methods

After receiving an explanation of the procedure and giving consent, 42 patients underwent cardiac catheterization and left ventriculography. Patients were studied supine in the fasting state 2 to 12 months after acute myocardial infarction to evaluate persistent chest pain or symptoms of congestive failure. The diagnosis of acute myocardial infarction was based on the clinical presentation, the development of Q or QS waves in the electrocardiogram of 0.03 second's duration and characteristic serial serum enzyme changes.

Left ventricular pressure was recorded with fluid-filled catheters, a P23D pressure transducer and a multichannel recorder. In all patients zero pressure was taken as that obtained 10 cm above the top of the table. Special care was taken to optimize the frequency response of the pressure recording system.[16] The system was thoroughly flushed to remove visible air bubbles. A screw clamp damping valve, with semirigid Tygon tubing (4 cm long; internal diameter 1/16 inch; external diameter 1/8 inch) running through it, has been employed for "critical damping" of pressure recordings in our laboratory. The pressure transducer is connected to one end of this valve. The catheter is attached to the other end of the valve by a three-way stopcock. A saline-filled syringe is also attached to this stopcock so that a "square wave" signal may be produced by maintaining constant manual pressure on the syringe while rapidly turning this pressure into and out of the transducer with the stopcock. The screw on the valve is tightened until minimal "undershoot" appears on the downstroke of the "square wave."

Simultaneous recordings of left ventricular pressure with undamped fluid-filled and micromanometer tip catheters in our laboratory have revealed that the diastolic pressure change between lowest early diastolic and end-diastolic pressures may be overestimated 15 to 30 percent by undamped fluid-filled catheters. For nine patients studied in our laboratory, the average diastolic pressure change obtained from "critically damped," fluid-filled catheters was only 1.6 mm Hg (7 percent) greater than the average diastolic pressure change calculated from micromanometer tip catheter tracings.

Left ventricular A wave amplitude was measured both from zero pressure (A_0) and from the pre-A wave pressure (A_{PAP}). Final A wave values were averages of A wave amplitudes measured from 10 consecutive cardiac cycles.

Values for left ventricular compliance were calculated from left ventricular volumes obtained from biplane angiograms taken at a rate of 6 or 12 frames/sec and left ventricular pressures recorded immediately before the angiograms. Angiograms were made after left ventricular pressure injection of 50 to 60 ml of 76 percent sodium and meglumine diatrizoate using a technique described previously for this laboratory.[17] Ventricular volumes were calculated during sinus rhythm by the area-length method.[18,19] Left ventricular end-diastolic and lowest early diastolic pressures were averaged from 10 consecutive cardiac cycles.

Left ventricular compliance was calculated from three formulas:

$$\Delta V/\Delta P \quad (1)$$

$$(\Delta V/ESV)/\Delta P \quad (2)$$

$$dV/dP_{ED} \times 1/EDV/BSA \quad (3)$$

where ΔV = the left ventricular diastolic volume change or the angiographic stroke volume calculated as the end-diastolic volume (EDV) minus the end-systolic volume (ESV) in milliliters; ΔP = the left ventricular diastolic pressure change calculated as the end-diastolic pressure (LVEDP) minus the lowest value for early diastolic pressure (LErDP); $\Delta V/ESV$ = the diastolic volume change divided by the end-systolic volume to calculate diastolic fractional volume change; dV/dP_{ED} represents the reciprocal of the slope of the diastolic pressure-volume curve at end-diastole and is calculated according to the method of Gaasch et al.,[20] which assumes a linear log-pressure versus volume relation and a constant positive pressure intercept at zero volume for all patients; BSA = body surface area in square meters.

The assumptions, advantages and limitations of these three formulas have been discussed in detail previously.[20,21]

Seven of the patients (Cases 1 to 3, 14, 19, 22 and 39, Table I) were studied by infusion of 200 to 600 ml of low molecular weight dextran (Rheomacrodex®). Left ventricular A wave amplitude measured from zero pressure, left ventricular diastolic pressure change (ΔP) and cardiac output were determined before infusion and after each 200 ml incremental infusion. Indicator-dilution (indocyanine green) cardiac output values were obtained by a method previously described for this laboratory.[22] Stroke volume or diastolic volume change ($\Delta V_{Ind.-Dil.}$) was calculated by dividing cardiac output by heart rate. Values for both diastolic pressure-volume slope ($\Delta P/\Delta V_{Ind.-Dil.}$) and A wave

TABLE I

Hemodynamic Data, Left Ventricular Volumes, Percent Abnormally Contracting Segments, Compliance Indexes and Left Ventricular A Wave Amplitudes in 42 Patients After Myocardial Infarction

Case no.	BSA (m^2)	EDV (ml)	EDV/BSA (ml/m^2)	ESV (ml)	ΔV (ml)	LV Mass (g)	EDP (mm Hg)	LErDP (mm Hg)	ΔP (mm Hg)	EF	% ACS	ΔV/ΔP (ml/mm Hg)	ΔV/ESV/ΔP (mm Hg^{-1})	$\frac{dV}{dP_{ED}} \times \frac{1}{EDV/m^2}$ (mm Hg^{-1})*	A_0 (mm Hg)	A_{PAP} (mm Hg)
1	1.86	234	126	176	58	210	11.0	1.0	10.0	0.25	27.2	5.80	0.033	2.80	27.1	16.0
2	1.88	168	89	78	90	162	8.0	−0.3	8.3	0.54	21.7	10.84	0.139	4.28	3.8	2.3
3	2.02	136	67	90	46	177	10.0	5.0	5.0	0.34	26.7	9.20	0.102	3.18	7.2	2.6
4	1.84	187	102	121	66	193	4.7	−0.7	5.4	0.35	14.9	12.22	0.101	8.90	4.2	.26
5	1.91	122	64	38	84	178	10.0	2.3	7.7	0.69	5.1	10.91	0.287	3.18	9.5	4.7
6	1.69	154	91	67	87	171	4.8	−1.3	6.1	0.56	6.4	14.26	0.213	8.64	4.0	3.2
7	1.70	140	82	50	90	118	14.5	1.0	13.5	0.64	9.2	6.67	0.133	1.96	14.4	5.5
8	1.88	136	72	64	72	198	10.9	6.5	4.4	0.53	2.3	16.36	0.256	2.84	11.5	4.0
9	1.61	226	140	146	80	209	16.2	6.3	9.9	0.35	37.9	8.08	0.055	1.70	18.1	11.1
10	1.86	181	97	66	115	199	8.3	1.3	7.0	0.64	4.6	16.43	0.249	4.07	1.11	7.9
11	1.50	207	138	158	49	153	28.0	18.0	10.0	0.24	34.6	4.90	0.031	0.86	28.6	20.0
12	1.76	246	140	208	38	437	26.0	5.2	20.8	0.15	39.4	1.83	0.009	0.94	30.8	6.3
13	1.75	126	72	88	38	165	7.0	−0.6	7.6	0.30	9.9	5.00	0.057	5.12	12.5	8.7
14	1.71	141	82	87	54	191	9.0	4.5	4.5	0.38	14.3	12.00	0.138	3.65	3.7	2.5
15	1.64	237	145	176	61	306	20.0	5.1	14.9	0.26	29.5	4.09	0.023	1.30	25.4	17.4
16	1.94	206	106	118	88	341	14.4	6.6	7.8	0.43	11.6	11.28	0.096	1.98	15.3	4.0
17	1.80	212	118	137	75	238	16.6	7.0	9.6	0.35	20.2	7.81	0.057	1.65	16.3	7.3
18	2.03	187	92	114	73	279	21.8	9.3	12.5	0.39	14.3	5.84	0.051	1.17	25.4	10.1
19	1.89	252	133	192	60	269	13.4	0.4	13.0	0.24	26.0	4.62	0.024	2.17	13.8	7.9
20	1.62	212	131	173	39	217	19.2	7.3	11.9	0.18	27.9	3.28	0.019	1.37	22.0	11.3
21	1.76	281	160	240	41	283	18.9	5.3	13.6	0.15	19.8	3.01	0.013	1.40	26.9	8.9
22	1.97	162	82	109	53	172	9.0	0.3	8.7	0.33	17.8	6.09	0.056	3.65	10.9	4.3
23	1.76	175	99	98	77	105	21.1	0.5	20.6	0.44	14.5	3.74	0.038	1.22	24.2	19.3
24	1.38	154	112	101	53	217	12.5	0.7	11.8	0.34	14.8	4.49	0.044	2.37	9.3	3.3
25	1.50	135	90	85	50	143	6.0	−1.2	7.2	0.37	24.8	6.94	0.081	6.32	12.4	4.6
26	1.81	120	66	66	54	171	10.0	−1.0	11.0	0.45	8.3	4.91	0.074	3.18	8.7	2.4
27	1.96	383	195	326	57	...	38.9	21.4	17.5	0.15	55.4	3.26	0.010	0.57	37.9	10.1
28	1.75	325	185	276	49	313	22.7	5.3	17.4	0.15	27.2	2.82	0.010	1.11	24.9	10.1
29	1.75	580	331	480	100	327	24.6	7.8	16.8	0.17	36.8	5.95	0.012	1.00	34.0	13.1
30	1.86	187	101	122	65	234	6.7	2.2	4.5	0.35	21.1	14.44	0.118	5.44	8.0	3.6
31	1.86	221	119	166	55	323	38.0	0.7	37.3	0.25	33.4	1.47	0.009	0.59	37.8	16.3
32	1.86	245	132	165	80	269	12.0	2.5	9.5	0.33	43.1	8.42	0.051	2.50	25.4	13.5
33	1.75	287	164	235	52	387	36.0	6.8	29.2	0.18	35.8	1.78	0.008	0.63	42.9	13.9
34	1.64	212	129	155	57	200	26.0	6.7	19.3	0.27	21.8	2.95	0.019	0.94	29.5	16.5
35	2.10	144	69	98	46	172	15.0	−0.2	15.2	0.32	31.1	3.30	0.031	1.88	39.1	29.0
36	1.96	230	117	156	74	217	10.5	0.0	10.5	0.32	29.5	7.05	0.045	2.98	10.4	5.7
37	1.64	199	121	155	44	200	33.0	11.0	22.0	0.32	18.6	2.00	0.013	0.70	36.3	14.5
38	2.04	230	113	144	86	322	10.0	0.2	9.8	0.37	11.0	8.78	0.060	3.18	10.5	5.8
39	1.78	146	82	77	69	168	11.9	−2.0	13.9	0.47	1.5	4.96	0.064	2.53	12.2	4.5
40	1.76	202	115	135	67	286	18.3	2.3	16.0	0.33	15.7	4.19	0.031	1.46	25.4	13.5
41	1.71	248	145	180	68	155	19.4	5.8	13.6	0.27	36.7	5.00	0.028	1.35	20.4	11.0
42	1.75	126	72	66	60	160	4.6	0.8	3.8	0.48	27.0	15.79	0.239	9.17	5.6	3.2

* All values in this column × 10^{-2}.

ACS = abnormally contracting segment; A_{PAP} = pre-A wave pressures; A_0 = left ventricular A wave amplitudes measured from zero; BSA = body surface area; dV/dP_{ED} = reciprocal of the slope of the diastolic pressure-volume curve at end-diastole; ΔP = left ventricular diastolic pressure change calculated as EDP minus LErDP; ΔV = left ventricular diastolic volume change or angiographic stroke volume calculated as EDV minus ESV; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; LErDP = lowest early diastolic pressure; LV = left ventricular.

amplitude were calculated from data collected from all seven patients before infusion and after each 200 ml incremental infusion. None of the patients studied by infusion had valvular insufficiency.

Segmental disease of the left ventricle, expressed as percent abnormally contracting segment (percent ACS), was determined from left ventricular biplane angiograms by the method of Feild et al.[23] The end-systolic perimeter of the left ventricular cavity was superimposed on the end-diastolic perimeter in both the anteroposterior and the lateral projections using a marker for the central X-ray beam and the lower border of the X-ray film. The percent of the total end-diastolic perimeter that was contracting abnormally or the percent abnormally contracting segment is the akinetic or dyskinetic length along the end-diastolic circumference divided by the total end-diastolic circumference. The end-diastolic ventricular perimeter and the length of the akinetic or dyskinetic segment were determined by a map measurer (Eugene Dietzgen Co.). The percent abnormally contracting segment in the anteroposterior and lateral views was averaged for the final value for each patient. Differences in percent ACS determined independently by two investigators ranged from 0.13 to 1.06 percent ACS (mean difference 0.45).

Left ventricular ejection fraction (EF) was calculated as the angiographic left ventricular stroke volume divided by the end-diastolic volume. Left ventricular mass was determined by the area-length and left ventricular wall thickness method of Rackley et al.[24]

The correlations in this study were expressed as r^2 values since many of the relations are not linear. In cases of nonlinear relations the hypothesis that the particular relation being examined was linear was tested and rejected at the 0.05 confidence level using an F test. The r^2 value, the square of the correlation coefficient, is the percentage of the total deviation in observed Y values about the mean Y value accounted for by the regression equation. An estimate of the predictive ability of the regression equation is given by the r^2 value.

Results

The left ventricular volumes, pressures, masses, $\Delta V/\Delta P$, ejection fractions, percent abnormally con-

TABLE II

Correlations Between Left Ventricular A Wave Amplitude and Indexes of Left Ventricular Compliance, Percent Abnormally Contracting Segments, Ejection Fraction, End-Diastolic Volume, End-Diastolic Pressure, and Mass

	Left Ventricular A Wave Amplitude	
	Measured from Zero Pressure (A_0)	Measured from Pre-A Wave Pressure (A_{PAP})
$\Delta V/\Delta P$ (ml/mm Hg)	$r^2 = 0.59$; $P = 2.8 \times 10^{-3}$; inverse quadratic	$r^2 = 0.28$; $P = 5.3 \times 10^{-3}$; inverse linear
$(\Delta V/ESV)/\Delta P$ (mm Hg^{-1})	$r^2 = 0.63$; $P = 1.2 \times 10^{-6}$; inverse quadratic	$r^2 = 0.31$ $P = 9.6 \times 10^{-4}$; inverse quadratic
$dV/dP_{ED} \times 1/(EDV/BSA)$	$r^2 = 0.72$; $P = 2.0 \times 10^{-7}$; inverse quadratic	$r^2 = 0.39$; $P = 2.0 \times 10^{-4}$; inverse quadratic
%ACS	$r^2 = 0.36$; $P = 1.2 \times 10^{-4}$; direct linear	$r^2 = 0.19$; $P = 4.0 \times 10^{-3}$; direct linear
EF	$r^2 = 0.43$; $P = 8.4 \times 10^{-5}$; inverse quadratic	$r^2 = 0.10$; $P = 0.043$; inverse linear
EDP (mm Hg)	$r^2 = 0.76$; $P = 1 \times 10^{-7}$ direct linear	$r^2 = 0.39$; $P = 1.6 \times 10^{-4}$; direct quadratic
EDV/BSA (ml/m^2)	$r^2 = 0.32$; $P = 2.5 \times 10^{-4}$; direct linear	$r^2 = 0.04$; $P = 0.04$; direct linear
EDV (ml)	$r^2 = 0.32$; $P = 2.7 \times 10^{-4}$; direct linear	NS
Mass (g)	$r^2 = 0.22$; $P = 0.002$; direct linear	NS

NS = no significant correlations; other abbreviations as in Table I.

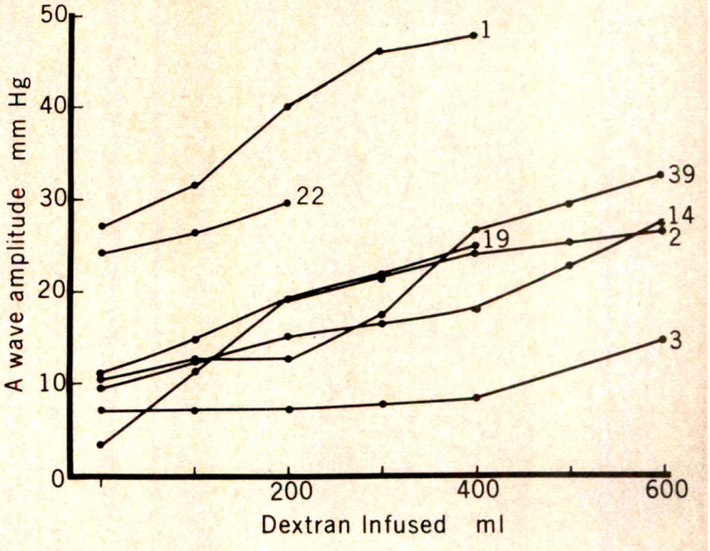

FIGURE 1. Left ventricular A wave amplitude in millimeters of mercury versus the volume of dextran infused in milliliters for seven patients after myocardial infarction.

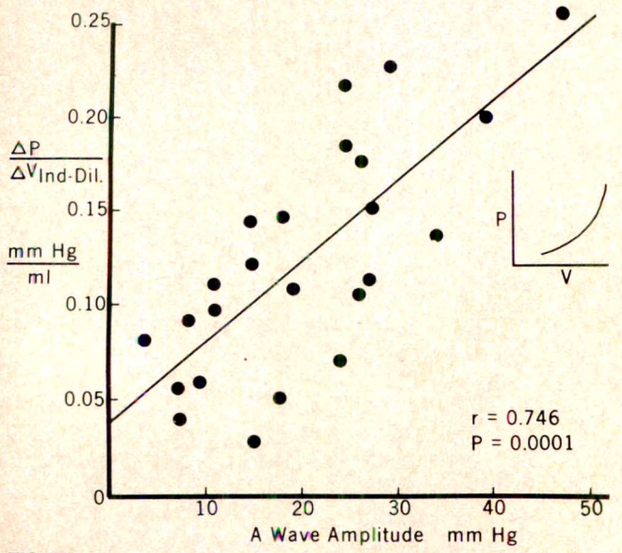

FIGURE 2. Values for diastolic pressure-volume slope ($\Delta P/\Delta V_{Ind.-Dil.}$) versus corresponding left ventricular A wave amplitudes for the seven patients given dextran infusions. Both $\Delta P/\Delta V_{Ind.-Dil.}$ and A wave height were obtained from data collected from the seven patients before infusion and after each 200 ml incremental infusion. ΔP = left ventricular end-diastolic pressure minus lowest early diastolic pressure; ΔV = diastolic left ventricular volume change.

tracting segments, three indexes of left ventricular compliance, left ventricular A wave amplitudes measured from zero (A_0) and the pre-A wave pressures (A_{PAP}) for the 42 patients studied after infarction are presented in Table I. A_0 has a direct quadratic relation with A_{PAP} ($r^2 = 0.72$; $P = 2.0 \times 10^{-7}$). The regression equation is $A_0 = -1.08 + 2.98\ (A_{PAP})$ minus $0.060\ (A_{PAP})^2$.

Correlation of A wave amplitude and measurements of compliance: Table II presents the type of relation and r^2 and P values for the correlations between A_0 and A_{PAP} and the three measurements of compliance, percent ACS, EF, EDV, EDV/BSA, EDP and LV mass. A_0 has high correlations with the three compliance indexes and lower but significant correlations with percent ACS, EF, EDV, EDV/BSA and LV mass. A_0 correlates inversely with the three compliance indexes and EF and directly with percent ACS, EDV, EDV/BSA and LV mass. A_0 has a high direct quadratic correlation with EDP. A_{PAP} has either lower or no significant correlation with all these variables.

A wave amplitude (A_0) increased after dextran infusion in all seven patients studied by infusion (Fig. 1). A wave amplitudes before infusion had significant relations with all three compliance indexes (r^2 values 0.68 to 0.82). Maximal postinfusion A wave amplitude had no statistically significant relation with any of the three compliance indexes although r^2 values ranged from 0.44 to 0.59. Maximal percent increase in A wave amplitude after infusion had a significant relation only with $dV/dP_{ED} \times 1/EDV/BSA$ ($r^2 = 0.86$; $P = 0.021$). The correlations with the other two compliance indexes were not statistically significant probably because of the small number of patients in the dextran infusion series.

Correlation of A wave amplitude and diastolic pressure-volume curve: Figure 2 presents a plot of diastolic pressure-volume slope values ($\Delta P/\Delta V_{Ind.-Dil.}$) versus their corresponding A wave amplitudes. $\Delta P/\Delta V_{Ind.-Dil.}$ and A_0 were measured from data collected from all seven patients before dextran infusion and after each 200 ml incremental infusion. An example of a left ventricular diastolic pressure-volume curve that could be obtained by making measurements over a range of pressures and volumes for a particular ventricle is shown in the inset. It should be appreciated that the ventricle would operate along only a segment of the curve under any particular set of circumstances. The statistically significant relation between A wave height and $\Delta P/\Delta V$ ($r^2 = 0.557$ or $r = 0.746$; $P = 0.0001$) indicates that an increase in left ventricular A wave amplitude produced by dextran infusion is associated with movement of the portion of the pressure-volume curve over which the ventricle is operating up the curve to a region of steeper slope. Thus, the slope of the diastolic left ventricular pressure-volume curve for any ventricle, as reflected by the compliance values, is a major determinant of the magnitude of change in A wave height for a particular volume of dextran infused.

For the 42 patients, $\Delta V/\Delta P$ correlated with $\Delta V/ESV/\Delta P$ ($r^2 = 0.74$; $P = 2 \times 10^{-7}$, linear) and $dV/dP_{ED} \times 1/EDV/m^2$ ($r^2 = 0.45$; $P = 3.4 \times 10^{-5}$, linear). $\Delta V/ESV/\Delta P$ had a direct quadratic relation with $dV/dP_{ED} \times 1/EDV/m^2$ ($r^2 = 0.42$; $P = 0.0002$). Percent ACS had significant relations with $\Delta V/\Delta P$ ($r^2 = 0.30$; $P = 6.5 \times 10^{-4}$, linear), $\Delta V/ESV/\Delta P$ ($r^2 = 0.70$; $P = 1.3 \times 10^{-6}$, cubic), and $dV/dP_{ED} \times 1/EDV/m^2$ ($r^2 = 0.23$; $P = 0.0029$, linear).

Discussion

The use of left ventricular pressures recorded immediately before left ventricular angiograms for the determination of left ventricular A wave amplitude and left ventricular compliance assumes that little change in pressure occurs during the period of left ventricular opacification at which time ventricular volumes are measured. Minimal changes in left ventricular end-diastolic pressure and end-diastolic and end-systolic volumes have been reported during ventricular opacification.[25] Similar observations using micromanometer tip catheters and left ventricular biplane cineangiograms have been made in our laboratory.

Diastolic pressure-volume relations: The relation between left ventricular pressure and volume or some index of ventricular dimensions, obtained either during diastole or during passive distension of the ventricle, has been reported to be curvilinear or exponential by some workers[5,26–31] and virtually linear by others.[32,33] In animal studies acute interventions such as intravenous administration of isoproterenol or methoxamine[27] and increasing the heart rate

to more than 180 to 200 beats/min[34] have produced configurational changes in control pressure-volume curves. However, neither stellate ganglion nor vagal stimulation has altered diastolic pressure-volume or pressure-myocardial segment length relations under various experimental conditions.[35–37] Thus, the diastolic pressure volume relation is subject to the conditions under which it is examined.

Because of the complexity of diastolic pressure-volume relations, several methods for quantitating these relations have been evaluated. Some workers[38] have used a simple ratio of simultaneous pressure and volume measurements (that is, EDV/EDP). Others[3,21,39,40] have assumed a linear pressure-volume relation for a portion of the diastolic interval (during atrial contraction or the period between the lowest early diastolic to the end-diastolic pressures). Another method consists of calculating the reciprocal of the slope of the pressure-volume curve at end-diastole assuming a linear log-pressure versus volume relation and a constant positive pressure intercept at zero volume for all subjects. In a study of left ventricular compliance changes in animals subjected to long-term volume overload, the relation between left ventricular end-diastolic pressure and end-diastolic diameter determined over a range of end-diastolic pressure was demonstrated to be essentially linear.[33] Hence, various types of linear diastolic pressure-volume relations have been useful in characterizing changes in ventricular compliance.

Evaluation of left ventricular compliance: The evaluation of left ventricular compliance in patients after myocardial infarction is complicated by the fact that both an increase in ventricular size and changes in the physical properties of the ventricular wall may result in decreased values for compliance. A reduction in compliance values secondary to an increase in ventricular size alone could result from a shift of the portion of the pressure-volume curve over which the ventricle is operating to a steeper segment of the same curve that existed before infarction. However, changes in the physical properties of the ventricular wall would alter the pressure-volume relation so that a higher level of pressure would be associated with any ventricular volume.

Thus, the compliance of ventricles of similar size could be adequately evaluated by a simple formula such as $\Delta V/\Delta P$ since variation in the physical characteristics of the ventricular wall would account primarily for differences in diastolic pressure-volume slopes for these ventricles. For our patients, however, end-diastolic volumes ranged from 64 to 331 ml/m^2 and ventricles of different sizes had similar values for $\Delta V/\Delta P$ (Table I). Differences in ventricular size are accounted for by $\Delta V/ESV/\Delta P$ (formula 2) and $dV/dP_{ED} \times 1/EDV/m^2$ (formula 3). Formula 2 incorporates fractional diastolic volume change, which is analogous to fraction volume changes measured in studies of pulmonary[41] and blood vessel[42] distensibility. In formula 3 a value representing the slope of a tangent to the pressure-volume curve at end-diastole is divided by EDV/BSA. However, values for formula 3 have a very high correlation with EDP ($r^2 = 0.96$) since both the natural logarithm of EDP and EDP itself are required for its calculation.

Despite the differences among the three compliance formulas, values for these formulas correlated significantly with one another. Values for these formulas have been demonstrated to be more sensitive to changes in the physical properties of the ventricular wall as represented by percent ACS than changes in ventricular size in postinfarction patients.[21] The selection of a particular formula for the evaluation of compliance would depend upon the objectives of the study, the methods available, the types of disease or experimental preparation being investigated, the duration of the disease (acute versus chronic), and the size of the ventricles.

Correlation of left ventricular A wave and compliance: A high inverse correlation between left ventricular A wave amplitude and left ventricular compliance might have been expected for patients studied after infarction because of the increased resistance to filling of diseased ventricles at the time of atrial systole and forceful left atrial contractions.[1,5,6] The similarity of the correlations between A wave height and all three compliance indexes may be related to two factors. First, A wave amplitude was demonstrated to have a significant relation with diastolic pressure-volume slope ($\Delta P/\Delta V$ or the reciprocal of formula 1) in the dextran infusion studies. Second, A wave amplitude had a relatively low correlation with EDV and EDV/BSA. Thus, one would not expect the correlations between the formulas that account for ventricular size (such as $\Delta V/ESV/\Delta P$) and A wave amplitude to be significantly higher than the correlation between pressure-volume slope and A wave height.

Elevations in left ventricular A wave height with dextran infusion were closely associated with increases in the steepness of diastolic pressure-volume slopes. These data corroborate the findings of high inverse correlations between A wave amplitude and the left ventricular compliance indexes measured in the 42 patients. Patients with larger left ventricular A wave heights have ventricles that are operating along steeper diastolic pressure-volume curves. Results of the dextran studies suggest that alterations in left ventricular A wave height due to acute interventions such as volume loading or diuresis may be used to estimate the slope of the pressure-volume curve for the ventricle being studied.

Correlation of left ventricular A wave and segmental disease: The significant relation between left ventricular A wave amplitude and extent of abnormally contracting segment (percent ACS) is probably related to the correlation of both of these variables to left ventricular compliance. The correlations between left ventricular A wave height and the compliance indexes were higher than the correlations between A wave amplitude and percent ACS. Two factors may be responsible for these results. First, A wave ampli-

tude has a very high correlation with left ventricular end-diastolic pressure ($r^2 = 0.76$), which is required for the calculation of compliance, whereas percent ACS has a much lower correlation with this pressure ($r^2 = 0.34$; $P = 2.4 \times 10^{-4}$, linear). The high correlation between A wave amplitude and left ventricular end-diastolic pressure might be expected since the energy expended during atrial systole would result in a greater increase in left ventricular pressure for any volume delivered to a less compliant ventricle.[1-6] Second, values for left ventricular A wave amplitude and left ventricular compliance are probably influenced both by the abnormally contracting segment as measured by ACS and small areas of fibrosis or ischemia in the ventricular wall outside the ACS.

The inverse relation between left ventricular A wave amplitude and ejection fraction demonstrated in our study suggests that augmentation of left ventricular end-diastolic fiber length by atrial systole may be particularly important in optimizing the performance of ventricles with decreased systolic function. The extent of left ventricular segmental disease after myocardial infarction apparently is responsible for both the increased stiffness of the ventricular wall, which is reflected in increased left ventricular A wave amplitude, and the decrease in systolic function of the ventricle.[43] Thus, increased left ventricular A wave amplitudes in patients after myocardial infarction denote a decrease in both left ventricular compliance and systolic performance.

Acknowledgment

We express our thanks to Mrs. Donna Chapman and Mrs. Kay Neel for their assistance in preparing the manuscript.

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Dynamic Characterization of Premature Ventricular Beats and Ventricular Tachycardias

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The contraction patterns induced by ectopic ventricular premature beats and ventricular tachycardias occurring in man during left ventriculography were analyzed. These were compared with contraction patterns induced by ventricular premature beats and tachycardias produced in five dogs by epicardial left ventricular apical or basilar stimulation. Two patterns of contraction observed in the animals corresponded to two patterns observed in man. Apically stimulated left ventricular beats produced an "hourglass" type of contraction pattern and were hemodynamically more effective than beats arising from basilar stimulation, which produced an inverse "teardrop" pattern. The same patterns were reproduced by experimental ventricular tachycardias. These observations stress the importance of a normal sequence of ventricular contraction to optimal cardiac function in man and warn against the hazards of misinterpretation of the left ventricular contraction pattern if the beat originates ectopically during ventriculography.

The hemodynamic consequences of ectopic cardiac stimulation were first described by Wiggers[1] in 1925. He believed that "a certain orderliness in the mode of contraction may be necessary in order to produce a maximal effect on intraventricular pressure." Further clinical interest in this subject was engendered by the advent of the permanent epicardial pacemaker lead for treating complete heart block. Complete agreement still does not exist as to the optimal site for epicardial pacing. Corday et al.[2] described both a "benign" and "malignant" ventricular tachycardia based upon the hemodynamic response to apical versus basilar stimulation of the left ventricle, respectively. Clinical left cineventriculography has confirmed that ventricular premature beats are associated with asynchronous patterns of contraction.[3]

The purpose of this report is to describe the various patterns of left ventricular contraction in catheter-induced ectopic beats during cardiac catheterization in man and to correlate these with the contraction patterns of ectopically stimulated intact dog hearts.

Material and Methods

Studies in Man

Left cineventriculograms with normal contraction patterns were selected from patients undergoing diagnostic cardiac catheterization. Ventriculograms were obtained in the 30° right anterior oblique position and recorded on 16 mm film at 60 frames/sec utilizing a 9 inch X-ray image intensifier system; 35 to 45 ml of 75 percent sodium and meglumine diatrizoate was injected over 2 seconds by a power injector through a catheter in the left ventricle.[4] The electrocardiogram and brachial arterial blood pressure were recorded simultaneously with the ventriculogram. An event marker system permitted exact matching of this graphic information with each cine frame, thus permitting accurate identification of ventricular premature beats. The ventriculograms included in this study had to meet the following criteria:

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1. A premature beat was studied if it followed a normally conducted beat, with which it was then compared.
2. If the premature beat occurred first, it was compared with a beat at least once removed from the immediate postextrasystolic beat.

The ventriculograms were projected to life-size dimensions based upon known catheter diameter. A normally conducted beat and a premature beat occurring during the same injection were traced frame by frame. Motion analysis was carried out by a method previously described[3] but, to minimize error, the minor axes drawn perpendicular to the long axis were considered as total segments rather than as hemisegments representing anterior and inferior wall contractions. This procedure will be further illustrated in the text. Ten ventriculograms in 10 patients with minimal or no coronary artery disease satisfied the criteria cited and were of sufficient radiographic quality to be included in the study.

Animal Experiments

The response of the left ventricle to ectopic stimulation was observed during multiple ventriculographic studies conducted in five dogs. Observations were made with both single ectopic beats and ventricular tachycardia. With the animals under general anesthesia, a thoracotomy was performed and pacemaker wires were sutured epicardially to the left ventricular apex, left ventricular outflow tract, right atrium and mid-right ventricle. A metal clip was placed on the myocardium at the site of each pacemaker wire. These wires were passed to the exterior through a stab wound in the chest and labeled as to site. A cannula inserted and fixed in the left atrium was also passed to the exterior and capped for future use. The dogs were permitted to recover and maintained in their quarters. They were studied 4 days to 2 weeks after operation according to the following protocol:

Anesthesia was provided with use of morphine-Nembutal® or morphine-chloralose and urethane. Each dog was intubated and put on a mechanical respirator and then secured to a rotating table top. The left ventricle was entered retrograde across the aortic valve with either a Statham SF1 catheter or a metal cannula fashioned from a large standard transseptal needle introduced by way of the carotid artery and connected directly to a pressure transducer. A standard catheter was placed in the aortic arch by way of the femoral artery.

The dogs were permitted to maintain their own sinus rhythm. An experimental triggered pacemaker was connected to each lead and programmed so as to deliver a premature stimulus after every third or fourth sinus beat. This instrument had a coupling interval adjustable from 0 to 1 second, a refractory interval adjustable from 0.1 to 10 seconds and a 2 msec pacemaker impulse adjustable from 0 to 25 volts. The degree of prematurity was regulated in successive studies so as to produce early and late premature ventricular beats. The intensity of the stimulus was adjusted to the lowest level that would produce a mechanical response. In the same animal, sustained ventricular tachycardia was produced from the same pacemaker sites and studied ventriculographically. The animal was placed in the right anterior oblique position. Hand injections of 20 to 30 cc of 75 percent sodium and meglumine diatrizoate were made through the left atrial cannula. The ventriculograms were recorded at 60 frames/sec. An average of six ventriculograms were obtained in each animal. A 20 minute interval between successive ventriculograms allowed subsidence of ventricular depression induced by the contrast agent. As in the human studies, each cine frame could be matched with pressure and electrocardiographic events through the use of an event marker.

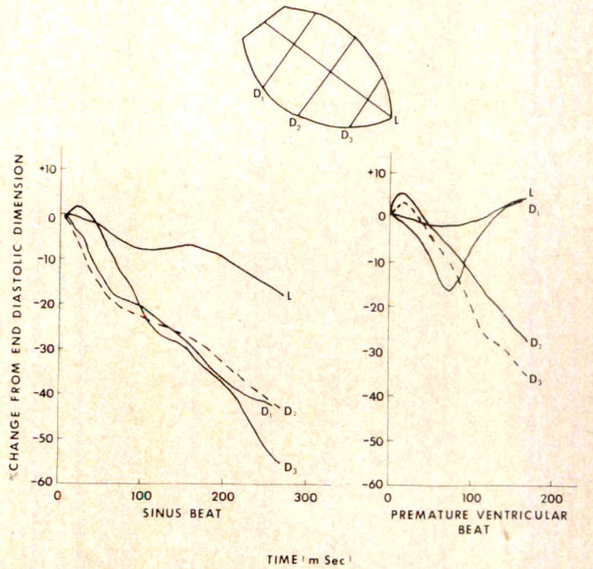

FIGURE 1. Comparison of the motion analysis of a sinus beat **(left)** with that of a premature ventricular beat **(right)** occurring in the same ventriculogram in a normal patient. The code for the segments involved is illustrated in the figure. L represents the long axis of the ventricle drawn from apex to the midportion of the aortic valve. D_1, D_2 and D_3 represent three minor axes constructed perpendicular to L quadrisecting the long axis. The percent change of each segment from its end-diastolic length is plotted against time. Expansion of a segment is plotted as a positive change from zero, and contraction or shortening as a negative change. In comparison with the sinus beat, the premature beat resulted in slight movement of the major axis and periapical asynchrony. This pattern is similar to that observed in experimental animals during epicardial stimulation of the apex.

Results

Studies in Man

Each premature beat that could be identified electrocardiographically as ventricular in origin produced an abnormal contraction pattern in comparison with its control beat. Figure 1 illustrates motion analyses of two beats from the same ventriculogram. The premature beat produced long axis akinesis and periapical asynchrony.

Figure 2, A and B, illustrates the left ventricular silhouette during control and ventricular premature beats in a patient with normal coronary arteries and hemodynamic status. The left ventricle has a "crenated" appearance during the ventricular premature beat and a symmetrical pattern of reduction in size during the normal beat. Even ventricular premature beats occurring with long sinus beat to premature beat intervals produce abnormal contraction patterns. Figure 3 graphically analyzes the motion of the beats drawn in Figure 2. In comparison to the control beat, the premature beat produces dyskinesis of all the minor axes with the only progressive shortening occurring in the major ventricular axis.

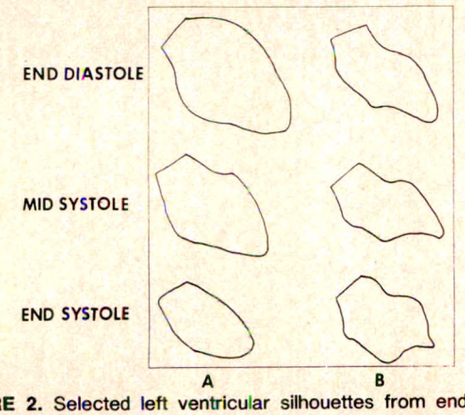

FIGURE 2. Selected left ventricular silhouettes from end-diastole, mid-systole and end-systole with a normal sinus beat **(A)** and a premature beat **(B)** in the same ventriculogram. Note the highly irregular and almost "crenated" appearance of the ectopically stimulated ventricle during contraction.

In general, ventricular premature beats tended to produce several distinctive contraction patterns. The two most often seen have already been illustrated. In Figure 1, contraction occurred mostly in the peribasilar and midportion minor axes. The periapical segment displayed asynchrony or dyskinesis, or both. The long axis exhibited minimal shortening. The net effect of this pattern would be to "propel" blood toward the apex. Another common contraction pattern of ventricular premature beats is illustrated in Figure 3 and has as its net effect the formation roughly of a globular shaped left ventricle with the long axis shortening at the "expense" of the minor axes.

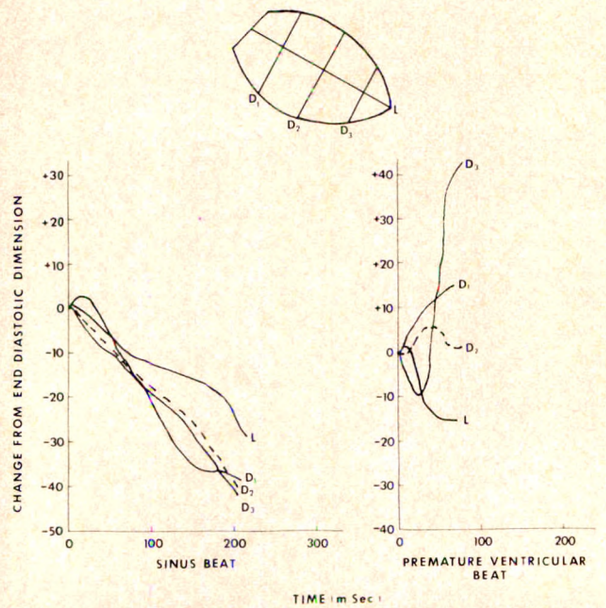

FIGURE 3. Motion analyses of the two beats drawn in Figure 2. There is paradoxical systolic expansion of all segments except the long axis.

Two runs of ventricular tachycardia were analyzed, but, unfortunately, the ventriculograms in these cases did not contain sinus beats for comparison. The ventricular contraction patterns induced by ventricular tachycardia did not differ appreciably from those observed during isolated ventricular premature beats. Beats occurring serially during ventricular tachycardia tended to produce a similar but not necessarily identical contraction pattern.

Studies in Animals

Ventricular premature beats: Adequate comparison between apically and basally stimulated left ventricular ectopic beats was made in two ventriculograms from each of three dogs. Stimuli applied to the left ventricle produced two distinct patterns of contraction depending on whether the apex or base was stimulated. In either instance, the initial salient feature was an expansion of the segment adjacent to the site of the stimulus. This pattern was observed regardless of the timing of the premature beat. Figure 4A illustrates selected silhouettes and a motion analysis of an apically stimulated ventricular premature beat. There was paradoxical systolic expansion of the periapical segments with vigorous contraction of the base and midportion of the ventricle. These findings should be contrasted with results of the premature beat illustrated in Figure 4B, taken from a subsequent ventriculogram in the same animal. In this case, the ventricle was stimulated by means of the wire attached to the left ventricular outflow tract. Here, the basilar portion of the left ventricle expanded paradoxically whereas the periapical portion contracted. From these two distinct contraction patterns simplified conceptual models may be constructed. Apical stimulation results in trapping of blood in the apical regions, whereas basilar stimulation results in a more globular left ventricular configuration with blood being sequestered in an expanded outflow tract region.

The hemodynamic correlates of apical versus basilar stimulation can be illustrated by comparison of the two beats cited. Table I shows the R–R interval for the normal control beat and the ventricular premature beat, left ventricular volumes and peak pressures for control and ventricular premature beats originating with apical and basilar stimuli. The data were derived from two sequential ventriculograms in one experimental preparation. Apical stimulation was more effective hemodynamically than outflow tract stimulation when beats with the same diastolic filling period were compared. Stimulation of the apex produced a greater percent of control aortic pressure and a larger ejection fraction than did stimulation of the base. This was true in all ventricular premature beats which appeared late enough to open the aortic valve. When the beats appeared too early to produce a rise in aortic pressure, the patterns of contractions were the same as those just described. When ejection of blood did not occur, early ventricular stimulation gave rise to an internal rearrangement of the ventric-

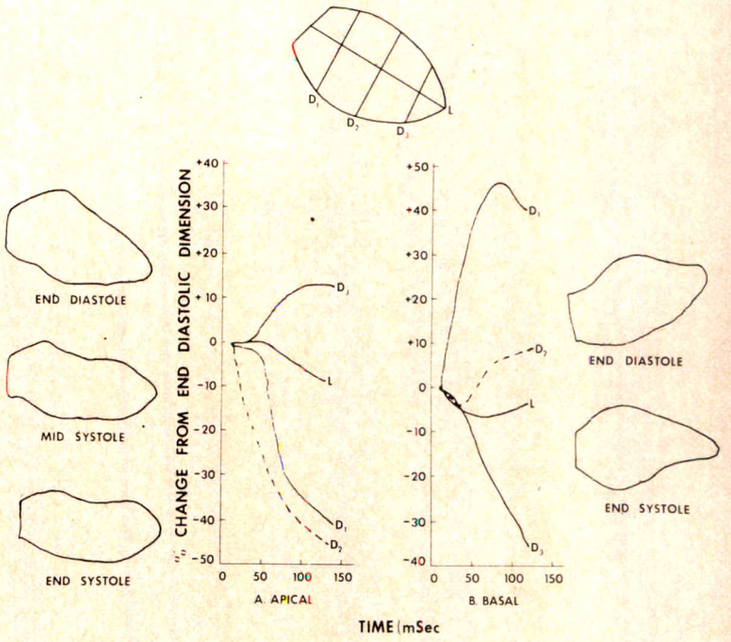

FIGURE 4. Selected silhouettes and motion analysis after apically stimulated **(A)** and basally stimulated **(B)** ventricular premature beats in a dog. Note the paradoxical systolic expansion of the periapical segment D_3 in **A** and the marked paradoxical expansion of the peribasilar segment D_1 in **B.**

ular contents. It is also possible that mitral regurgitation occurred with these beats.

Ventricular tachycardia: Experimental ventricular tachycardia was produced by stimulating the left ventricular apex or base at a rate sufficient to drive the ventricle (190 to 210 beats/min). The ventriculograms obtained during the arrhythmia showed patterns similar to those produced by single ventricular premature beats in each area. However, when the ventricle was apically stimulated, there tended to be more paradoxical expansion in the long axis than with the single ventricular premature beat. Figure 5A shows a sequence of four silhouettes during a typical beat of apical ventricular tachycardia. In mid to late systole, the lengthening of the major axis and the circumferential contraction of the midportion of the left ventricle about the minor axis gave an "hourglass" appearance to the left ventricular cavity. This was most notable when the ventriculogram was projected at normal film speed. Ventricular tachycardia produced by stimulation of the base showed expansion of the basilar area with normal shortening of the major axis. The ventricle became more globular in appearance, resembling an inverse teardrop with the point toward the apex. Selected silhouettes drawn from the ventriculogram obtained during a basally stimulated ventricular tachycardia beat are shown in Figure 5B.

Discussion

The apparent regional expansion of the stimulated portion of the left ventricle has been noted by others.[5,6] Our study confirms these observations for left ventricular apical and basilar ventricular premature beats and tachycardias. The general patterns of contraction observed are unrelated to preload, diastolic filling periods, or even the presence or absence of aor-

TABLE I

Effect of Site of Pacemaker on Left Ventricular Performance

Site	Interval (msec) Normal R–R	Interval (msec) R–R (VPB)	LV Pressure Peak (mm Hg)	LV Pressure % of Control	LV Volumes (ml) EDV	LV Volumes (ml) ESV	LV Volumes (ml) SV	EF
Control	376	...	96	...	49	18	31	0.63
LV apex	...	288	80	83	50	27	23	0.46
Control	380	...	116	...	52	18	34	0.65
LV base	...	288	86	74	46	33	13	0.28

EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; SV = stroke volume; VPB = ventricular premature beat.

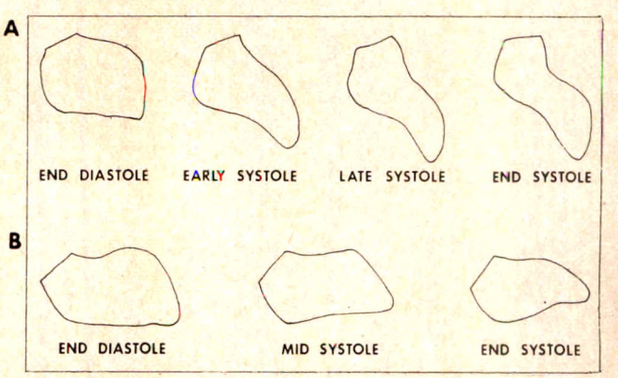

FIGURE 5. Left ventricular silhouettes during experimental tachycardia. See text for details.

tic ejection, but are determined solely by the point of stimulus application.

The relative importance of ventricular asynchrony and the temporal relation between atrial and ventricular activation in producing a hemodynamic deficit with epicardial pacing has been studied in the dog heart. Daggett and co-workers[7] compared atrial, atrioventricular and right ventricular epicardial pacing in a dog preparation. They demonstrated that atrioventricular pacing at properly adjusted intervals tended to override hemodynamically the adverse effect of having the ventricular impulse applied ectopically. From this observation they concluded that the interval between atrial and ventricular systole was a more important determinant of ventricular function during cardiac pacing than the site of entry of the impulse to the ventricle. In another series of experiments, Daggett et al. utilized the isovolumic left ventricle to study the hemodynamic effects of pacing from various epicardial sites. They showed that better performance was obtained with stimulation of the left ventricular apex than with stimulation of the right ventricle. However, their study did not mention the influence of atrioventricular sequential pacing in the intact heart when the pacing site was varied on the left ventricle itself. In our study, the production of single ventricular premature beats showed a hemodynamic and morphologic difference depending upon stimulus site when diastolic filling time was constant. This mechanism should be independent of atrial systolic–ventricular systolic interval (As–Vs) in experiments of the type illustrated in Table I. It is conceivable that basilar stimulation may produce more mitral regurgitation than apical stimulation even at fixed As–Vs intervals, since these patterns of contraction are so different. In our animal experiments, quantification of mitral regurgitation was not possible since the injections were made by way of the left atrium to avoid unwanted stimulation of the ventricle during injection of dye.

In the dog experiments, there was a constant directional hemodynamic difference between apical and basilar stimulation of the left ventricle. Stimulation of the apex resulted in a greater percentage of aortic pressure even when R–R intervals and end-diastolic volumes were constant. This finding is in contradistinction to some earlier observations.[8,9] Our data emphasize the hemodynamic importance of synchronous ventricular contraction patterns that operate independently of atrial transport function. Experimentally produced asynchrony with its attendant shortened ejection time vitiates the Starling effect. In the one example listed in Table I, the end-diastolic volumes of the control and apically stimulated beat were practically the same, but the ejection fraction of the latter beat was considerably reduced.

Our study encompassed observations on similar phenomena in man and dogs. During clinical diagnostic ventriculography, the occurrence of ventricular premature beats is commonplace. Careful examination of a number of these beats revealed two major contraction patterns that were similar to those evoked with epicardial stimulation in dogs. It is difficult to make a direct comparison of these patterns in man to those in experimental animals since the exact stimulus site in each clinical case is unknown. A catheter passed retrograde across the aortic valve may stimulate the outflow tract by direct contact or stimulate the apical region by a jet stream of contrast material during the injection. To relate the two aspects of this study, two assumptions must be made: (1) that endocardial stimuli induce the same contraction pattern as epicardial stimuli, and (2) that in the human observations, the stimulus sites were indeed similar to those applied in the experimental animals. The minimal conclusion to be drawn from the human observations is that ventricular premature beats in man vary in their associated patterns of left ventricular contraction and that these may be categorized.

Clinical implications: Our study showed that ventricular stimulation either of the single ventricular premature beat type or of the repetitive tachycardia type results in a similar pattern of contraction. The observation that apically induced ventricular premature beats are more hemodynamically effective than basilar ventricular premature beats supports the concept of Corday et al.[2] that ventricular tachycardias may be benign or malignant depending upon their site of origin within the ventricle.

Some of the contraction patterns observed in our study bore great similarity to those seen during sinus rhythm in patients with segmentally diseased or ischemic ventricles.[10] The slower ventricular tachycardias occurring during ventriculography in the normal patient might lead to an erroneous diagnosis of asynergy. Our results emphasize the importance of maintaining and documenting normal sinus rhythm before assessing a left ventricular contraction pattern from the ventriculogram. If ectopic beats occur, it is essential to recognize them as such. In our study, it was possible to identify the site of application of a stimulus to the dog's left ventricle by the type of contraction pattern produced. Interpretation of ventriculograms in which ectopic beats occur can be subject to serious error.

Acknowledgment

We acknowledge the help of Drs. C. W. Urschel and E. H. Sonnenblick for their criticism of this work.

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Surface Recording of Electrical Activity from the Region of the Bundle of His

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In 16 dogs, by appropriate filtering and digital averaging on a PDP-9 computer, we were able to enhance the detection of electrical activity of interest in the P–R segment of the electrocardiogram. In instances (1) when such activity in the surface record coincided temporally with the internal recording from the bundle of His area, (2) when, with atrioventricular nodal block, the electrical activity of interest continued to be associated with the internally recorded His bundle deflection and not with atrial activity, and (3) when, with production of transmission delay between the bundle of His and the ventricle, the surface signal of interest continued to be associated with the internal His bundle deflection, a common signal source was considered likely. In certain instances the surface signal of interest in the P–R segment occurred well after the internally recorded His bundle deflection but about 15 msec before the earliest evidence of ventricular activity. In these instances, when the tests cited were applied and the blip of interest was associated with ventricular activity, the origin of the blip was thought to be in the region of the bundle branches.

In the 16 animals studied, one or more pieces of the evidence described were present to localize the origin of the signal. In seven animals, the signal was thought to originate from the bundle of His, in six from the region of the bundle branches and in three from both the bundle of His and bundle branches.

Since Scherlag and co-workers first described the catheter technique for recording His bundle activity in the dog[1] and in man,[2] there has been a renaissance in extracellular approaches to electrophysiologic-electrocardiographic correlations. Interest in the subject has been intense and reporting logarithmic, especially regarding diagnostic and prognostic information now available in the fractionated P–R segment.

During the course of multiple lead, high-speed, high-frequency surface recordings for other purposes, we noted apparent cardiac electrical activity in the P–R segment. The possibility that the activity might arise from the conduction system below the atrial level but above the ventricular level, and still be accessible through noninvasive means, seemed worthy of exploration.

Figure 1 is an example of the type of data that aroused our interest. The top recording is from a surface site on the chest of a dog slightly anterior to the anterior axillary line in the fifth intercostal space. The middle record is a bipolar intracardiac electrogram recorded from a site near the bundle of His, and the bottom tracing is from the conventional V_5 position, although inverted. A 2:1 block at the atrioventricular (A–V) node is indicated by the failure of the second pacemaker impulse to be conducted below the atrial level. The His bundle deflection from the intracardiac lead and electrical activity of interest in the P–R segment (referred to as $blip_1$ [B_1] and $blip_2$ [B_2]) are ab-

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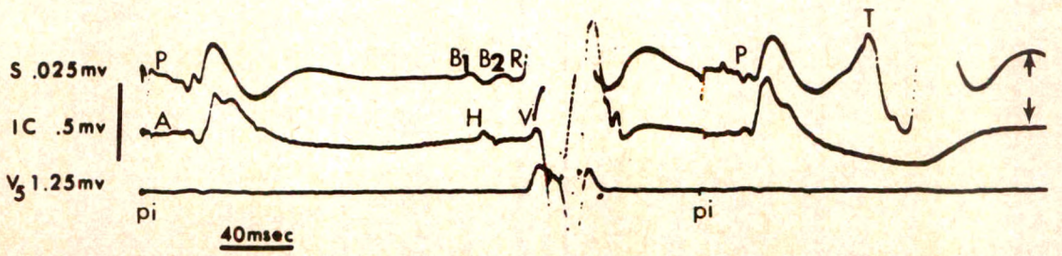


FIGURE 1. An amplified surface (S) lead filtered between 30 and 600 Hz **(top),** an intracardiac (IC) lead recorded from a site near the A–V junction **(middle)** and a surface-recorded conventional but inverted V_5 lead **(bottom)** from a dog exposed to a halogenated hydrocarbon. A = internally recorded atrial activity; B_1 and B_2 = blips of interest in surface P–R segment; H = His bundle activity; P = atrial activity; pi = pacer impulse; R = surface ventricular activity; T = surface-recorded ventricular recovery; V = internally recorded ventricular activity.

sent at the expected point in time, noted by the arrows. This finding suggests that the site of origin of B_1 and B_2 is somewhere below the level of A–V block.

The decreased rate of rise and overall amplitude of the His bundle signals from the internal lead can be attributed to the fact that this animal was one of a series in a study on the toxic effects of halogenated hydrocarbons known to have this effect on the His bundle deflection. The 50 beat computerized averages seen in Figure 2 exemplify an effort to amplify the P–R segment in another animal from the same series of toxicologic experiments.

Methods

In 16 healthy mongrel dogs—4 anesthetized with morphine sulfate and pentobarbital and 12 with pentobarbital alone—intubation and controlled respiration and normal base-line blood gas values were established. A bipolar pacing catheter was introduced transvenously into the high right atrium, and an intracardiac recording catheter capable of recording from three bipolar sites—1 mm, 1 cm or 1.1 cm apart—was introduced to the region of the bundle of His by the technique described by Scherlag et al.[1] An intra-arterial luminal catheter was introduced retrograde from the left femoral artery and positioned just distal to the aortic valve near the coronary ostia for delivering medications; an intravenous catheter was positioned in the inferior vena cava for similar purposes.

Pacing was instituted from the bipolar pair of recording electrodes that recorded the largest biphasic His bundle deflection, and the chest was mapped in order to find the site of maximal negative and maximal positive potential from the pacemaker impulse. These points were identified on the chest and usually lay to the left and anterior for the maximal positive deflection, and to the right, slightly higher and posterior for the maximal negative deflection. It was hoped that these peak positive and negative points also approximately defined the electrical axis of the bundle of His, which should roughly parallel the axis generated by these electrodes (Fig. 3). The identification of such a site should

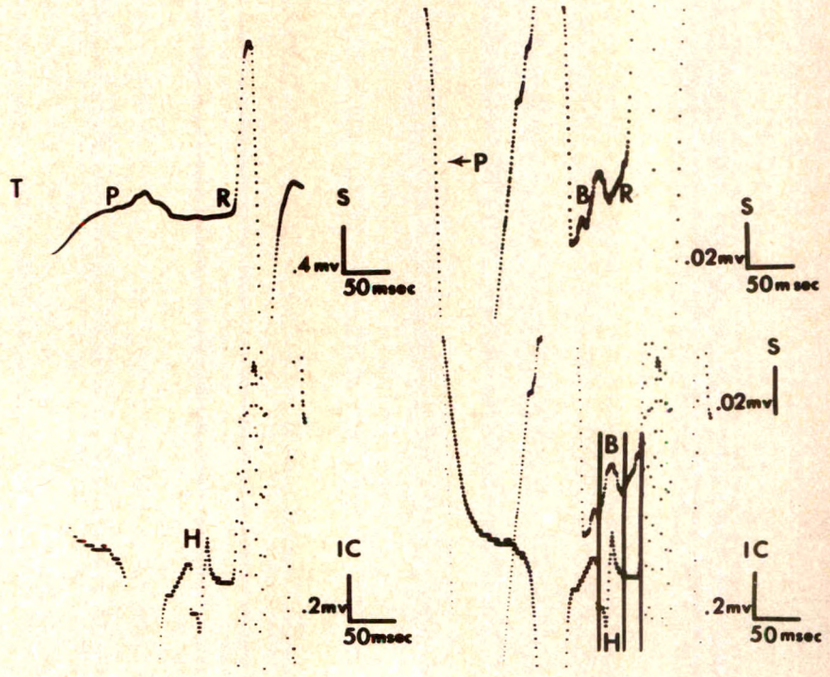


FIGURE 2. These 50 beat averages, taken at a sampling rate of 2,000/sec, are illustrative of our efforts to amplify the P–R segment in another animal from the same series of toxicologic experiments. At the **top left** is the surface signal; at the **bottom left,** the intracardiac recording from the His bundle area. The **top right** shows the amplified P–R segment with the surface blip of interest labeled B. The **bottom right** shows the temporal association of the surface signal of interest above, and the intracardiac recording from the His bundle region below. B = surface blip of interest in P–R segment; H = internally recorded His bundle activity; IC = intracardiac lead; P = surface-recorded atrial activity; R = surface-recorded ventricular activity; S = surface lead; T = surface-recorded ventricular recovery.

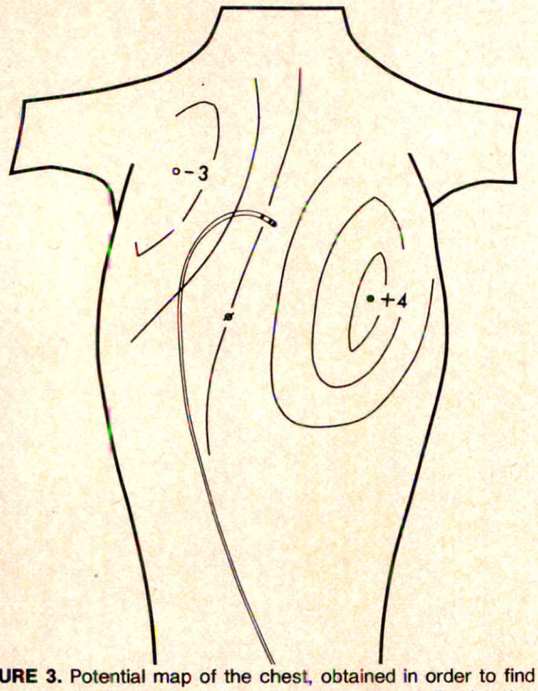


FIGURE 3. Potential map of the chest, obtained in order to find the site of maximal negative and maximal positive deflection from a pacemaker impulse originating from the bipolar pair of recording electrodes that had recorded the largest biphasic His bundle deflection. See text.

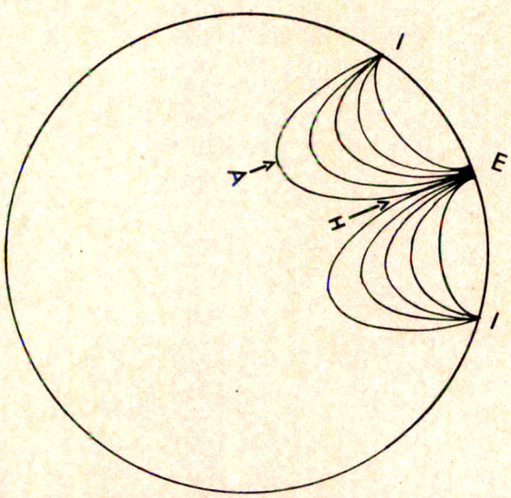
help to optimize the chance of correspondence between the most parallel current flow lines of the His bundle and the lead field of an exploring electrode (Fig. 4).

An arrangement of electrodes of the bipolar probe type was then designed with an exploring center surrounded by five indifferent points, connected by resistances to give a balanced bipolar configuration (Fig. 5). The site of the exploring electrode was placed at the point of peak positivity, and the immediate vicinity was searched for an area that gave a repetitive surface deflection at approximately the same time as that of the His spike in the intracardiac electrogram. A similar search was performed on the negative side.

The surface signal from the exploring electrode was fed into a Tektronix 26A2 differential amplifier and amplified 100,000 times, filtered between 0.1 and 3,000 Hz initially, and finally with a low-frequency cutoff between 1 and 80 Hz and a high-frequency cutoff of 600 Hz. Time synchronization was achieved by a special triggering network that also served to trigger the PDP-9 computer for averaging. After analog to digital conversion, either single cardiac cycles or 50 or fewer averaged beats were displayed on a storage oscilloscope for analysis and hard copy preparation. The constantly recorded signal on an Ampex FR 1300 tape recorder was available for later analysis, further averaging or preparation in hard copy form of sequential cycles photographed by a Grass oscilloscopic camera (Fig. 6).

Results

Figure 7 shows a recording from the intracardiac (IC) lead above, and the surface (S) recording below at a pacing rate of 90 beats/min. The blip of interest in the P–R segment is labeled. The initially prolonged conduction time of 76.6 msec from the low atrium through the A–V node (A–H interval) is accounted for by the anesthesia induced by morphine and pentobarbital. The base-line conduction time from the bundle of His to the earliest evidence of ventricular activity (H–V interval) was 31.6 msec. In the surface recording, the atrial to blip (P–B) interval was even longer than the A–H interval since atrial activity is detected earlier on the surface. From the surface blip of interest in the P–R segment to the earliest onset of ventricular activity (B–R), the time lapse was 20 msec. With pacing, the A–H and P–B intervals increased proportionately, whereas the H–V



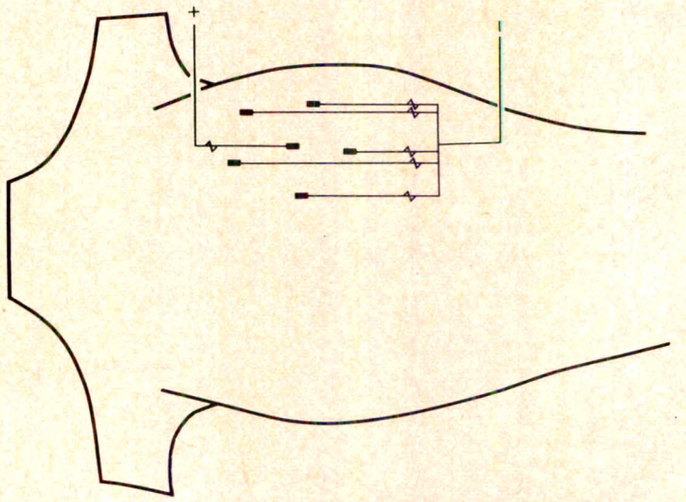


FIGURE 4 (left). Diagram of the lead field search for the surface electrode site that had optimal intersection with the most parallel flow lines from the His bundle and was least optimal for interfering atrial activity. A = hypothetical atrial activity; E = exploring electrode; H = hypothetical lead axis of His bundle; I = indifferent electrode.

FIGURE 5 (right). Bipolar probe type of arrangement of electrodes with a central exploring electrode surrounded by five indifferent electrodes connected through balanced resistances. See text.

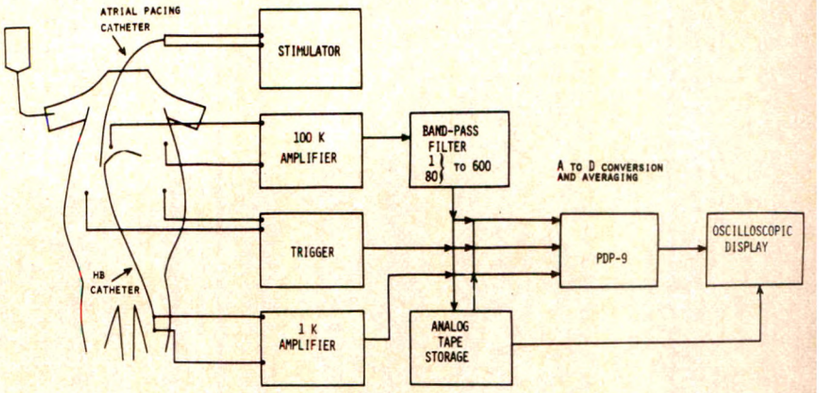


FIGURE 6. Diagram of mode of amplifying, filtering and displaying surface signal from exploring electrode. A = analog; D = digital; HB = His bundle; K = 1000; PDP-9 = computer. See text.

and B–R intervals remained fixed. As A–V nodal delay increased with the increased pacing rate, the surface blip of interest emerged as a discrete electrical phenomenon seen in the lower panel. The origin of the surface blip is difficult to ascertain. The shorter duration of the B–R interval compared to that of the H–V interval suggests that the blip might have arisen from one of the bundle branches rather than from the bundle of His. On the other hand, much of the apparent shortening in the B–R interval is due to greater ability of the more distal surface lead to detect the earliest evidence of ventricular activity when compared with the much more local His bundle electrogram with its constricted lead field.

Efforts were made to remove the atrial activity from the region of interest by causing first degree A–V block by administration of propranolol as demonstrated in Figure 8. The bottom pair of records are 50 beat averages of the intracardiac electrogram, and an average of the same 50 beats recorded from a surface lead, identified by the probe technique. The top two records represent the same lead and surface counterpart after administration of 10 mg of propranolol, also a 50 beat average. As the A–H interval spreads, note how B_1 and B_2 fail to move with the atrial activity, but seem to continue to be associated with the intracardiac His bundle deflection and ventricular activity. The timing of B_1 in the cycle with respect to its relation to ventricular activity and to the internally recorded His bundle activity suggests that the blip probably represents surface evidence of His bundle activity. B_2 probably arises from lower down in the conduction system.

Figure 9 demonstrates results of an effort to remove ventricular activity from the area of interest by causing conduction delay between the His bundle and the ventricle with administration of procainamide. The top sample is the intracardiac electrogram; the second is the surface counterpart after administration of 750 mg of procainamide. The third record is the intracardiac lead demonstrating H–V prolongation after administration of 1,500 mg of procainamide. Continued association with the surface deflection is seen, with the blip moving neither with atrial nor with ventricular activity but with the His deflection. The B–R intervals are in each instance 7.5 msec shorter than the intracardiac H–V counterparts. The phenomenon can be accounted for in this animal solely by the earlier appearance of ventricular activity as recorded from the surface. The slight difference in appearance of the surface evidence of atrial activi-

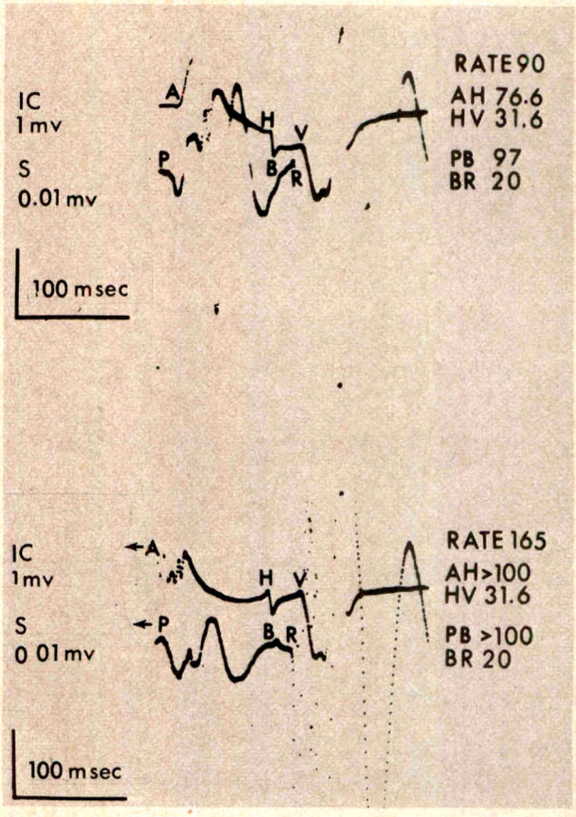


FIGURE 7. Simultaneous recording of intracardiac (IC) and surface leads at a pacing rate of 90 beats/min **(upper tracing)** and 165 beats/min **(lower tracing).** A = internally recorded atrial activity; AH = atrial-His interval; B = blip of interest in P–R segment; BR = blip-ventricular interval; H = His bundle activity; HV = His–ventricular interval; P = atrial activity; PB = atrial–blip interval; R = surface-recorded ventricular activity; S = surface lead; V = internally recorded ventricular activity. See text.

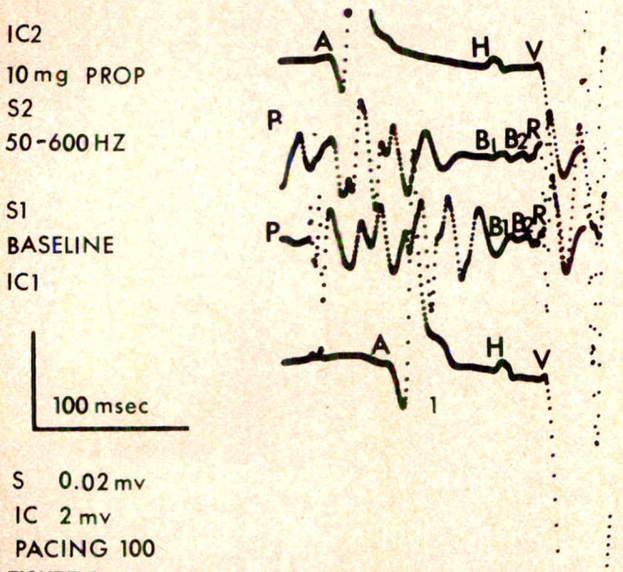


FIGURE 8. Intracardiac lead and surface electrogram before **(bottom pair)** and after **(top pair)** administration of 10 mg of propranolol. A = internally recorded atrial activity; B_1 and B_2 = blips of interest in surface P–R segment; H = His bundle activity; IC = intracardiac lead; IC_1 = base-line intracardiac lead; IC_2 = intracardiac lead after 10 mg of propranolol; P = surface-recorded atrial activity; PROP = propranolol; R = surface ventricular activity; S_1 = base-line surface lead; S_2 = surface lead after 10 mg of propranolol; V = internal ventricular activity. See text.

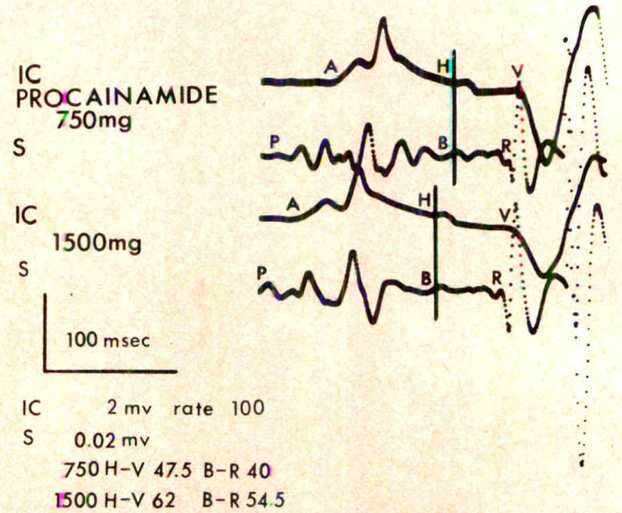


FIGURE 9. Intracardiac lead and surface electrogram after administration of procainamide in doses of 1,500 mg **(bottom pair)** and 750 mg **(top pair).** A = internally recorded atrial activity; B = blip; BR = blip–ventricular interval; H = His bundle activity; HV = His–ventricular; IC = intracardiac; P = surface-recorded atrial activity; R = surface-recorded ventricular activity; S = surface lead; V = internally recorded ventricular activity. See text.

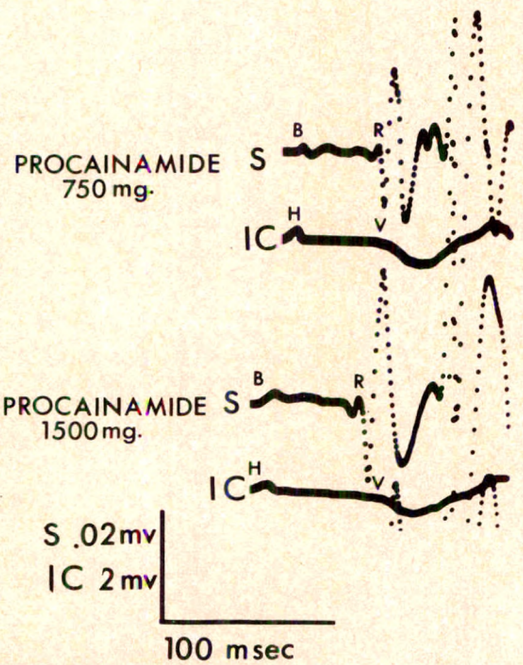


FIGURE 10. Recording of surface lead and intracardiac electrogram from another dog after administration of procainamide in doses of 1,500 mg **(bottom recording)** and 750 mg **(top recording).** B = surface blip of interest; H = His bundle activity; IC = intracardiac lead; R = surface-recorded ventricular activity; S = surface lead; V = internally recorded ventricular activity. See text.

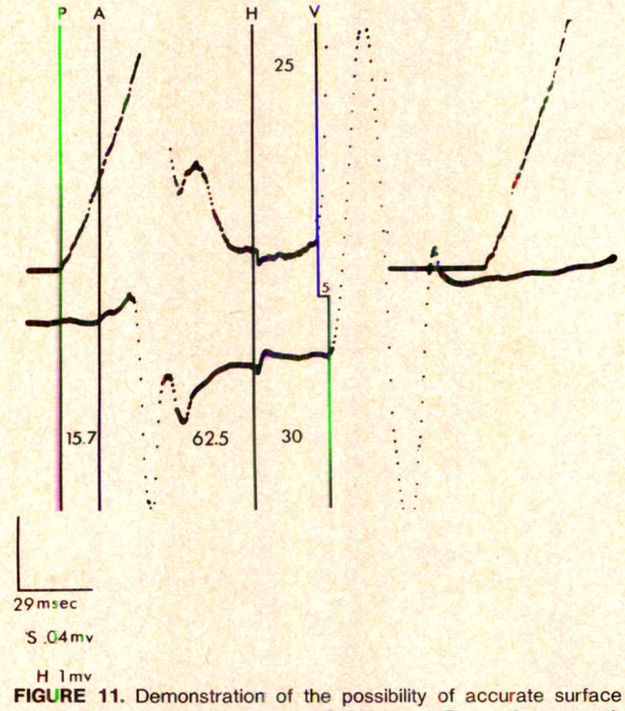


FIGURE 11. Demonstration of the possibility of accurate surface measurements of the fractionated P–R interval. The surface recording **(top)** and the internal recording **(bottom)** are each averages of the same 50 cardiac cycles. The shorter surface His-ventricular interval is accounted for by the earlier appearance of ventricular activity viewed from the surface. Intervals are in msec. AH = atrial–His interval; H = His bundle activity; HV = His–ventricular interval; PA = high to low right atrial interval; S = surface lead; V = ventricular activity.

ty at the two dose levels can be explained by the fact that the low-frequency cutoff at the time of the 750 mg dose of procainamide was 30 Hz, whereas the low-frequency cutoff at the time of the 1,500 mg dose was 10 Hz. The synchronizing lines were determined by computer with reference to the trigger and should represent true simultaneity.

Figure 10, from another animal, again demonstrates the movement of a deflection recorded from the surface lead (S) with the His bundle deflection recorded from the intracardiac lead during progressive and comparable B–R and H–V prolongation with administration of additional amounts of procainamide.

Discussion

Verification of suspected His bundle activity in amplified surface P–R segment: There are three ways of attempting to verify the origin of electrical activity recorded in the surface P–R segment. The first is simply temporal association with a carefully verified internal event. The success or believability of this means of verification depends upon an interference-free record and relative lack of activity on either side of the surface recording of alleged His bundle activity and upon an appropriate interval between this deflection and the onset of ventricular activity (Fig. 11). Because the surface evidence of ventricular activity always precedes internal evidence of such activity by 5 to 11 msec, the interval between the suspected surface His bundle activity and surface evidence of ventricular activity is necessarily shorter than that recorded from the internal lead. However, if the interval is within acceptable ranges, and if the surface signal does not significantly precede the internal His bundle signal, but coincides with it or is only slightly later, there is circumstantial evidence for a common origin of these signals. More supporting evidence is presented if, in addition, atrial pacing can cause A–V nodal transmission delay and consequent prolongation of the intracardiac A–H interval, and if the alleged His activity on the surface remains associated with the verified His activity from the internal lead. Rather convincing evidence is offered if, further, with pacing at a constant rate, and pharmacologic intervention with agents that remove atrial activity from the region of the His bundle by introducing A–V nodal delay or remove ventricular activity from His bundle activity by introducing His–ventricular delay, the electrical events of interest in the surface lead continue to associate themselves with the His bundle deflection from the internal lead.

It is important to eliminate any possibility of signal leak from amplifier to amplifier since this is a known hazard in multiple lead, simultaneous recording. This possibility was carefully eliminated in our series of experiments by physically removing the internal catheter and verifying the persistence of the surface signal.

Implication: As facility is achieved in finding the optimal surface recording site, and as a volume of experience with configuration and timing of internally verified surface signals is accumulated, the examination of the amplified surface P–R segment should become an important addition to the noninvasive approaches of cardiac evaluation.

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Microelectrode Study of Wenckebach Periodicity in Canine Purkinje Fibers

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Electrophysiologic mechanisms responsible for Wenckebach periodicity produced experimentally in a segment of blocked canine Purkinje fibers were investigated with multiple microelectrode recordings. Transmission through the zone of block was electrotonic. The Wenckebach mechanism was related to a progressive decrease in the efficacy of the transmitted electrotonic potential as a stimulus for the regenerative response at the distal block boundary with successive impulses of the cycle. This was manifested in the transmembrane potentials as a progressive decrease in upstroke velocity and a voltage change that caused the electrotonic potential to become progressively removed from the threshold for stimulation. The immediate cause of this phenomenon was a progressive increase in the voltage level (more negative) from which the electrotonic potential originated and a resulting change in voltage-dependent membrane resistance that further attenuated the signal with successive impulses of the cycle.

Two main mechanisms appeared to be responsible for these phenomena: (1) a progressive increase in maximal repolarization voltage (more negative) of the transmembrane potential, and (2) a progressive decrease in the diastolic interval that, in the presence of enhanced phase 4 diastolic depolarization, caused the voltage level from which the electrotonic potential originated to become further removed from the stimulation threshold with successive impulses of the cycle.

Previous studies from this laboratory have attempted to formulate concepts of block mechanisms in terms of observed phenomena manifested in the transmembrane potential recorded throughout segments of blocked canine ventricular conduction tissue.[1–4] Our initial investigations indicated that such studies must be performed in preparations with a defined segment of block not exceeding a critical length. A suitable preparation was developed using an electrical depolarizing current in which the magnitude of block could be critically controlled by varying the intensity of the blocking current.[1,3]

Wenckebach periodicity has been previously demonstrated experimentally and clinically in the atrioventricular (A–V) junction,[5–10] distal intraventricular conduction system[11–13] and ventricular myocardium.[12,13]

This type of cyclic conduction disturbance has most often been produced experimentally by overdrive at rapid rates, although it has been demonstrated in experimental microelectrode studies at slower rates of stimulation.[7,14–16] The mechanism of Wenckebach periodicity has previously been attributed to progressive encroachment upon refractoriness of the preceding impulse,[5,6] "decremental conduction" [10,11,16] or progressive inhomogeneity of electrical wave fronts in multifibered cardiac tissue.[7,15] It has also been suggested that a concealed (abortive) form of reentry may occur continuously throughout the Wenckebach cycle producing progressive prolongation of the P–R

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interval and an eventual nonconducted impulse.[17,18] This phenomenon involves the induction of progressive refractoriness.

Our investigations of mechanisms of second degree conduction disturbances operative over an entire spectrum of stimulation rates have explored variables that have previously been given little attention. In these studies we have used a preparation in which the length of the blocked segment is limited so as to constitute an elementary block unit, thus simplifying data interpretation.

Extensive microelectrode investigations in these *blocked segments* have revealed no data that might be interpreted as "decremental conduction" or "slow active propagation," and we are not convinced that these phenomena have actually been demonstrated in published reports.

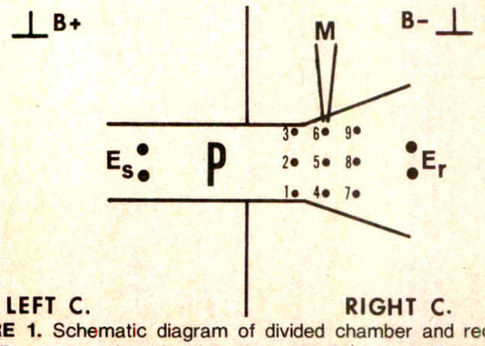

FIGURE 1. Schematic diagram of divided chamber and recording sites. B− = negative blocking electrode; B+ = positive blocking electrode; C. = chamber; E_r = bipolar recording electrode; E_s = bipolar stimulating electrode; M = recording microelectrode; P = the preparation, which was threaded through a small hole in the rubber partition separating the right and left chambers; numbers 1 through 9 = sites from which microelectrode recordings were taken in each experiment.

Method

Eighteen adult dogs weighing from 10 to 15 kg were anesthetized with 30 mg/kg of sodium pentobarbital. A lateral incision was made in the fourth intercostal space and the heart was rapidly excised. The left ventricular posterior false tendon along with conducting fibers of the posterior division of the left bundle branch were carefully dissected and placed in a divided Lucite® chamber filled with oxygenated Tyrode solution maintained at 37° C with a thermistor temperature controller. Composition of the Tyrode solution in millimoles per liter was sodium chloride 137.0; sodium bicarbonate 12.0; sodium phosphate 0.18; magnesium chloride 0.5; potassium chloride 2.7; calcium chloride 2.7 and glucose 5.5. The chamber was a rectangular well composed of two compartments separated by a thin latex membrane. The dimensions of each compartment were 1.5 by 1.0 by 0.45 cm. The flow rate was adjusted to 4 ml/min in each half of the chamber. The false tendon was threaded through a small preformed hole in the membrane separating the two chambers. The anatomic proximal portion of the preparation from which the microelectrode recordings were obtained was located in the right side of the chamber (Fig. 1). The Purkinje fibers of the preparation were stimulated at a rate of 1.0 to 2.0 cycles/sec from the left side of the chamber with a small bipolar electrode (E_s, Fig. 1). The stimulus consisted of a 4 to 10 volt square wave of 1 msec duration delivered by a Grass stimulator and isolation unit. Although Wenckebach cycles could readily be produced at slower stimulation rates, the rates cited were desirable for routine use because of enhancement of automaticity by the blocking current. An electrogram was obtained with a small bipolar electrode (E_r, Fig. 1) from the functional distal portion of the preparation in the right side of the chamber. It is apparent that the location of the preparation in the chamber was such that conduction occurred in an anatomic retrograde fashion throughout the experiments.

An electrical blocking current was supplied by a 280 volt battery source. The positive polarizing electrode (B+, Fig. 1) was placed in the left side of the chamber and the negative polarizing electrode (B−, Fig. 1) in the right side of the chamber. The current strength was regulated by a rheostat.

Transmembrane action potentials were obtained with glass capillary microelectrodes filled with 3M potassium chloride by boiling under vacuum. Electrodes with a resistance of 5 to 10 megohms were used in these experiments. The first stage input consisted of high impedance, capacitance neutralized amplifiers (NF-1, Bioelectric Instruments, Inc.). The indifferent electrode was placed in the right side of the recording chamber near the preparation. Liquid-metal junctions were made with silver-silver chloride electrodes. A square wave voltage calibrator was placed between solution and ground.

Time marks were supplied by a Tektronix time mark generator. The entire experiment was taped on a four channel analog tape recorder (Hewlett Packard 3960) and records were filmed both directly and from the tape at various voltage gains and sweep speeds for more defined measurements. A Tektronix 565 oscilloscope with both Polaroid® and 35 mm strip film was used for these procedures.

The experiments were performed under a dissecting microscope with a magnification of 12.5. Anatomic distance determinations were made with use of a graduated eyepiece.

Results

During application of the electrical blocking current a segment of block approximately 3 to 4 mm in length was produced by depolarization in the right chamber where the negative blocking electrode was located. The functional proximal boundary was located near the dividing partition. The exact delineation of the distal boundary was inherently difficult to determine, but would correspond to the site of the earliest regenerative response initiated by passive electrotonic transmission through the segment of block. Electrotonic potentials continued beyond the distal boundary as prepotentials preceding active responses. The transmembrane action potentials were usually normal in the more distal portions of the preparation. Differences of blocking effect in the various fibers of the preparation contributed to the problem of distal boundary localization.

Three sequential microelectrode recordings were obtained at 2, 3 and 4 mm locations from the dividing membrane producing a matrix of nine impalements (Fig. 1). By applying the appropriate amount of blocking current, Wenckebach cycles were produced and recorded at the various points. Figure 2 demonstrates an example of typical three cycle Wenckebach periods recorded from each of the nine positions dur-

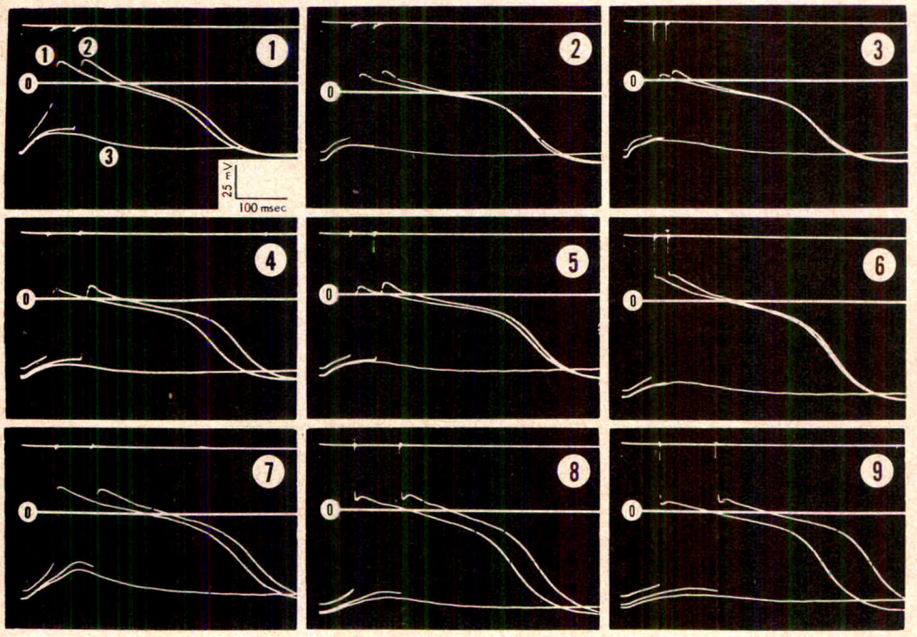

FIGURE 2. Experiment 6. Intracellular microelectrode recordings of three cycle Wenckebach periods taken from each of the nine sites labeled in Figure 1. Top tracing in each panel represents distal electrographic recordings. Zero millivolts is represented by 0 in each panel. In panel 1 the numbers 1 and 2 refer to the first and second responses with associated electrograms and 3 refers to the nonpropagated impulse.

ing a single experiment. Each cycle was photographed by superimposing successive sweeps of the oscilloscope. The superimposed stimulus artifacts initiating the three impulses are seen at the left edge of the top tracing in which the distal electrogram is displayed. The respective distal responses recorded by the microelectrode and corresponding electrogram are labeled 1 and 2 and the nonconducted impulse is labeled 3 without a corresponding electrogram. Variation in delay between the first and second impulses of the cycles resulted from separate applications of the blocking current at each site. Slight changes in the steady state of the preparation altered the effect of the blocking current requirement which was critical to produce the Wenckebach cycles. The first two complexes of each cycle, representing conducted impulses, exhibit a two component wave form. The initial deflection represents an electrotonic potential that originated from the proximal boundary of the blocked zone. The second delayed component represents a retrograde electrotonic potential originating from the regenerative response at the distal block boundary.[1,3] The third complex of each cycle that failed to attain threshold at the distal boundary is nonconducted and exhibits only an initial electrotonic component. The second component is absent because no regenerative response occurred. Some inhomogeneity of blocking effect in the various fibers is evident.

Phase 4 diastolic depolarization was always marked near the distal block boundary in the presence of the blocking current. The nonconducted electrotonic potential had relatively little effect upon the slope of phase 4 depolarization between the last conducted impulse and the first impulse of the succeeding cycle.

Figure 3 shows the variables measured in this experiment for the impulses of each Wenckebach cycle. An electrogram (EG) is displayed in the top tracing. The second tracing represents zero millivolt potential obtained by withdrawing the microelectrode from the fiber during application of the blocking current. The bottom tracing represents the recorded transmembrane potential. The various

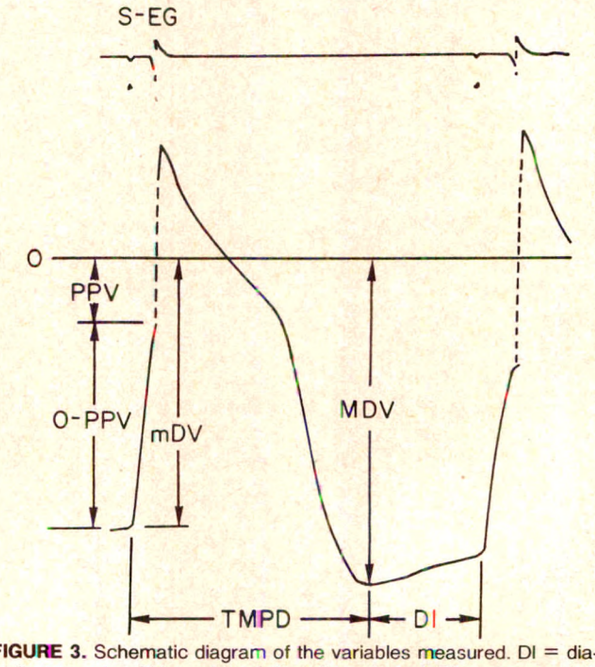

FIGURE 3. Schematic diagram of the variables measured. DI = diastolic interval; mDV = minimal diastolic voltage; MDV = maximal diastolic voltage; O–PPV = onset to peak prepotential voltage; PPV = peak prepotential voltage; S–EG = stimulus to electrogram delay; 0 = zero millivolt potential.

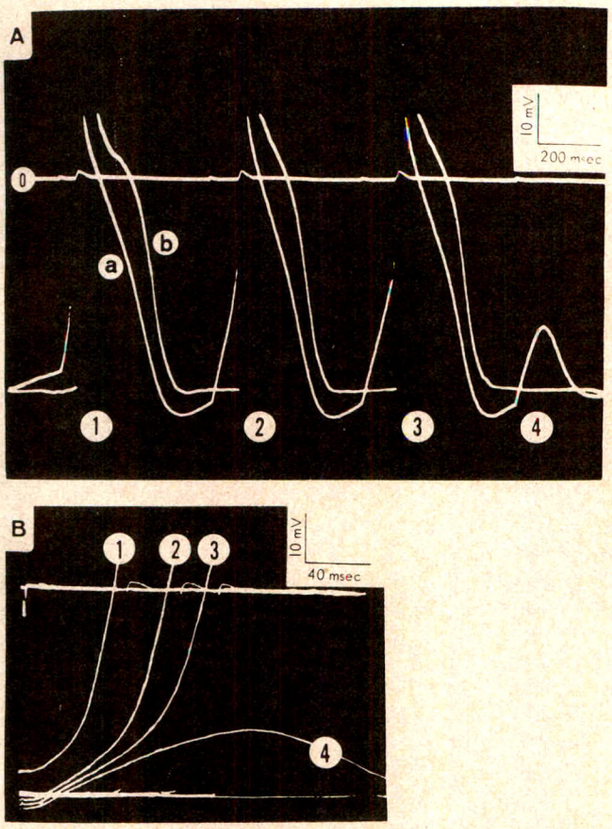

FIGURE 4. Experiment 12. Two fibers impaled in the vicinity of position 7 (see Fig. 1). Position b is 1 mm distal to position a. Zero millivolt potential (0) and distal electrogram are recorded in the top tracing. Numbers 1, 2, 3 and 4 represent four consecutive impulses of a four cycle Wenckebach period. **Panel A** displays the simultaneous microelectrode recordings of both positions. **Panel B** represents the superimposed initial components of recording positions a and b displayed at a greater sweep speed.

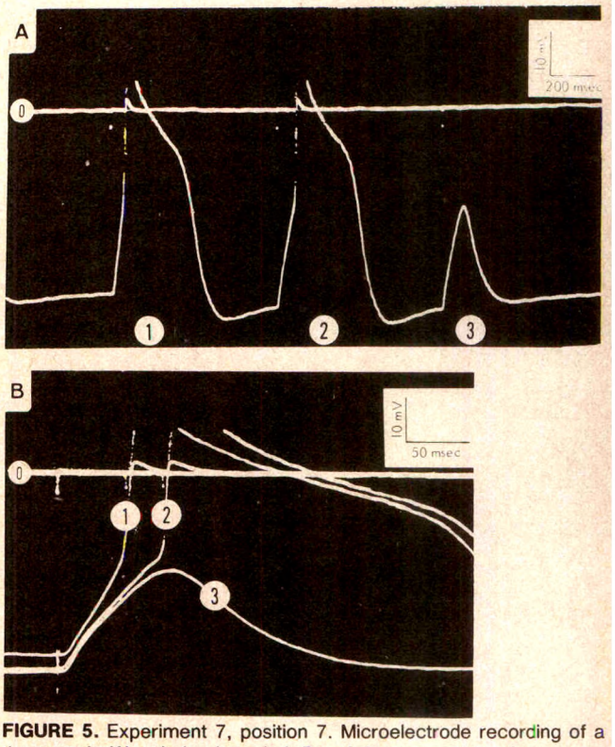

FIGURE 5. Experiment 7, position 7. Microelectrode recording of a three cycle Wenckebach period. **Panel A** represents a slow sweep speed used to visualize impulses 1, 2 and 3 of the Wenckebach cycle. Zero millivolt potential and distal electrogram are recorded in the top tracing. **Panel B** is a superimposition of the initial components of the three responses photographed at a more rapid sweep speed.

voltage and time variables measured are labeled and are as follows: The *minimal diastolic voltage* (mDV) represents the magnitude of the potential at the time the artificial stimulus was applied. The *maximal diastolic voltage* (MDV) represents the maximal negative voltage level attained after a response. The *peak prepotential voltage* (PPV) represents the negative voltage magnitude at the peak of the initial electrotonic potential. The *onset to peak prepotential voltage* (O–PPV) represents the onset to peak voltage of the initial electrotonic potential. The *transmembrane potential duration* (TMPD) represents the total time from the onset of the response to its recovery of maximal diastolic voltage. The *stimulus to electrogram response* (S–EG) represents the time delay between the stimulus and the electrogram. The *diastolic interval* (DI) represents the interval between the maximal diastolic voltage and the onset of the subsequent response. The slope of phase 4 diastolic depolarization was also examined.

Cycles containing up to 10 impulses were recorded, but 95 percent of the total number of cycles recorded contained fewer than 7 impulses. Three impulse Wenckebach cycles were the most easily produced and with few exceptions were recorded at each recording site in all experiments. The increment in delay with successive impulses was frequently inconsistent in the longer cycles, often not conforming to the classic Wenckebach structure. Because of inhomogeneity of block in the various fibers, one would not expect to see all significant determining voltage variables at every recording site in the complex, multifibered preparation. This is demonstrated in Figure 4, A and B, in which two areas of the preparation are simultaneously impaled. Fiber a is at a location equivalent to position 7 (Fig. 1). The second impalement, b, is recorded 1 mm distal to position 7. Figure 4A represents a slow sweep speed recording of a four impulse Wenckebach cycle and Figure 4B a superimposed fast sweep recording of each successive impulse in the cycle. Examination reveals that recording from position a demonstrates electrotonic prepotential activity and marked changes in slow phase 4 depolarization compared to findings in the recording from position b. A marked electrotonic response to the nonconducted impulse (4) is seen at position a, whereas position b demonstrated no electrotonic response. In this figure two microelectrode recording sites are separated by 1 mm and there is considerable variation in recorded activity. This finding suggests that the electrodes are in different fibers and demonstrates the dissociation that may occur under conditions of block even though the tissue acts as a functional syncytium in the normal state.

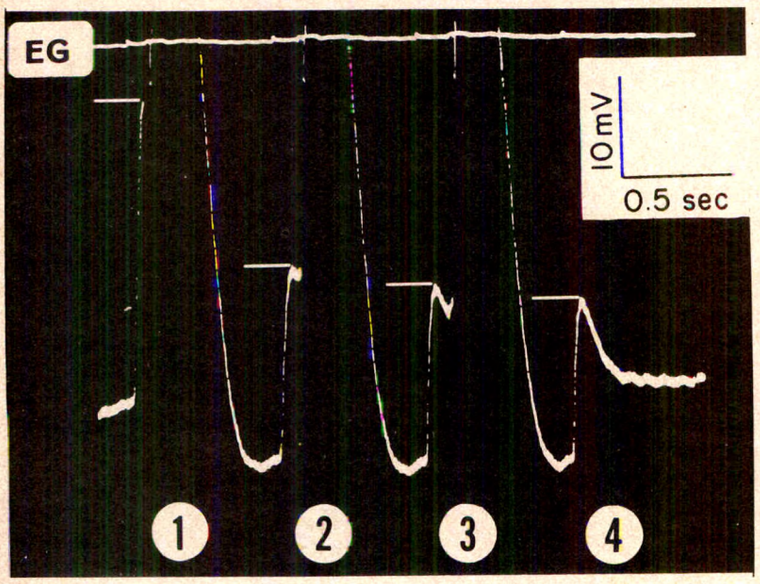

FIGURE 6. Experiment 9, position 3. Single fiber recording of a four cycle Wenckebach period recorded at high gain to demonstrate progressively increasing (more negative) peak prepotential voltages. Numbers 1, 2, 3 and 4 represent each successive response to artificial stimulation. EG represents the channel displaying the stimulus and distal electrogram. The voltage level at the peak of each prepotential is delineated by a small white line to the left of each peak.

Since three cycle Wenckebach periods were most commonly observed, a typical cycle is displayed in Figure 5, A and B. The data in Figure 5A were recorded at a slower sweep speed than those of Figure 5B. Two conducted responses are shown by the distal electrogram. The third impulse failed to conduct. The top tracing in each panel represents the zero millivolt potential as well as the distal electrogram. Examination of the first impulse of the cycle reveals a considerable increase in maximal compared to minimal diastolic voltage. Furthermore, the maximal diastolic voltage after the second impulse of the cycle exhibits slightly greater negativity than that after the first impulse. In the absence of a significant change in the slope of phase 4 diastolic depolarization this phenomenon would cause a progressive increase in minimal diastolic voltage with successive impulses of the cycle. This progressive change in maximal diastolic voltage with successive impulses was observed in many of the recorded Wenckebach cycles. Of particular importance was the marked increase in maximal compared to minimal diastolic voltage associated with the first impulse of the cycle. This consistently observed phenomenon was related to the marked increment of delay associated with the second impulse of the cycles.

Another frequently observed phenomenon may be seen in the four cycle recording (a) of Figure 4A and in Figure 6. A progressive decrease in diastolic interval with successive impulses of the cycle is apparent. This usually resulted from a progressive increase in transmembrane potential duration of each preceding impulse of the cycle caused by an increment in delay of the impulse which was manifested in the transmembrane recording as an increased duration of the initial electrotonic potential. In the presence of a relatively constant slope of phase 4 diastolic depolarization this would result in a progressive increase in minimal diastolic voltage with each impulse of the cycle. A decrease in diastolic interval was infrequently observed without a measurable increase in minimal diastolic voltage. This phenomenon appeared to be due to a slight change in the slope of phase 4 diastolic depolarization in some recordings. It could also have been due to the critical anatomic specificity for optimal recording of voltage variables at the distal block boundary in the multifibered preparation. Changes in the contour of the terminal portion of phase 3 at times made accurate evaluation difficult.

An almost constantly observed change throughout the recorded cycles was a progressive increase in minimal diastolic voltage with successive impulses of the cycle. This is apparent in Figures 4B and 5B and in some cycles in Figure 2. The greatest increase always occurred between the first and second impulses of the cycle. High gain recording was sometimes necessary to demonstrate the change in the later impulses of the cycle, and the phenomenon was usually more marked at several recording sites than in others in each preparation. Further examination of the figures reveals an equally constant feature consisting of a progressive decrease in the upstroke velocity of the initial electrotonic potential with successive impulses of the cycles. The greatest change was apparent between the first and second impulses.

A progressive increase in peak prepotential voltage with successive impulses of the Wenckebach cycle was observed in most recordings. This change is obvious in Figure 6 and to a lesser extent in Figure 5A. As with the previously mentioned observations, the change was often more marked at some recording sites than in others in each preparation. It was usually accompanied by a progressive decrease in onset to peak prepotential voltage, which was associated with the previously described changes in minimal diastolic voltage. This phenomenon appears to be related to

the voltage-dependent changes in membrane resistance described by Weidmann.[19]

Discussion

Concepts of Block Associated with Conduction Delay

An understanding of the electrophysiologic variables that appeared to be determinants of the Wenckebach structure in our study would be facilitated by some familiarity with our concepts of block associated with simple delay. These have previously been described in detail[1] and will be summarized.

Our initial studies[1] indicated that investigation of block mechanisms should be performed in a preparation with a segment of block limited in length so as to include a defined distal boundary. The presence of a distal boundary is necessary for wave form generation and for determination of block magnitude. The importance of such a preparation has recently been reemphasized by Cranefield et al.[11] Our data indicate that a blocked zone may be characterized as an inactivated fiber segment with proximal and distal active boundaries. Active propagation ceases at the proximal block boundary and transmission through the blocked zone is accomplished by a passive electrotonic potential that preserves continuity of conduction in simple delay. The transmitted electrotonic potential is the stimulus that initiates a regenerative response at the distal block boundary. Delay is incurred as a function of distance attenuation of upstroke velocity and voltage of the electrotonic potential dictated by the fiber cable properties. Severe attenuation so that the electrotonic potential fails to reach the threshold potential at the distal block boundary results in complete block. Stimulation of a regenerative response at the distal block boundary initiates a second electrotonic potential that is transmitted in a retrograde fashion back into the blocked zone to be superimposed upon the initial electrotonic potential. This potential also demonstrates distance attenuation of voltage and upstroke velocity. This phenomenon gives rise to a characteristic two component wave form of the transmembrane potential which is always recorded within a segment of simple block. Multiple components in the wave form suggest a more complex situation with fragmentation. The existence of this mechanism does not suggest that wave form components may not be caused by adjacent asynchronously excited fibers, which is almost surely the case when fragmentation occurs in a multifibered syncytial preparation; however, the two component wave form could be derived within a single fiber.[20]

Conduction abnormalities have often been ascribed to "decremental conduction."[10,11,16,21] This mechanism was hypothesized as a possible explanation for the "physiologic delay" found in the A–V node and was characterized as conduction in which the properties of the fiber change along its length in such a manner that the action potential becomes progressively less effective as a stimulus to the unexcited portion of the fiber even though the fiber is still excitable. Hoffman and Cranefield[16] further suggested that this type of conduction might be produced in other portions of the conduction system by a variety of pathologic conditions, although they did not restrict the possibilities to this mechanism. Hoffman et al.[21] made a distinction between "decremental conduction" and "slow conduction" per se. A third possibility would then be a predominantly electrotonic mechanism. Extensive microelectrode recordings throughout blocked segments in our series of experiments suggest the latter mechanism. Mendez and Moe previously described similar wave forms and emphasized their electrotonic origin between active and inactive regions of block in the A–V node[22] and Purkinje-papillary muscle preparations.[23]

We have never observed data that might be interpreted as "decremental conduction," as described, or "slow active conduction." The existence of delay between two recording points does not permit inference of the mechanism by which the delay was incurred. This requires extensive microelectrode recording throughout the area of block between the two recording points. In our opinion an actual documentation of "slow active propagation" would require demonstration of a progressive delay in *onset* of an active response as a distance function through an area of block.

Electrotonic wave form components: The electrotonic nature of the transmembrane potentials that we have always observed in blocked segments is indicated by the expected progressive distance attenuation of voltage and upstroke velocity and, of particular importance, a lack of delay in *onset* of the deflections throughout the blocked zone. A simultaneous onset of the initial electrotonic component throughout the blocked segment is somewhat distorted by a distance factor inherent in traveling wave theory which we have previously emphasized.[3] Early loss of high-frequency components results in a slight "apparent" delay in onset of the deflection with greater distances which may be particularly misleading with low gain recording.

We have accumulated conclusive evidence that the second electrotonic wave form component is derived from the regenerative response at the distal block boundary. This is indicated by the expected distance attenuation with retrograde transmission and the fact that the onset of the distal regenerative response precedes the onset of the attenuated signal in the more proximal portions of the blocked segment. The fact that this also is only an "apparent" delay in onset does not negate an inference as to the origin of the deflection. The second component is always present when a distal active response has been initiated and is always absent with nonconducted impulses. Furthermore, as the magnitude of delay is changed, which is easily accomplished by manipulation of the blocking current density, the onset of this component always maintains a temporal relation with the distal active response. The result of this phenomenon is that the observed duration of the initial electrotonic

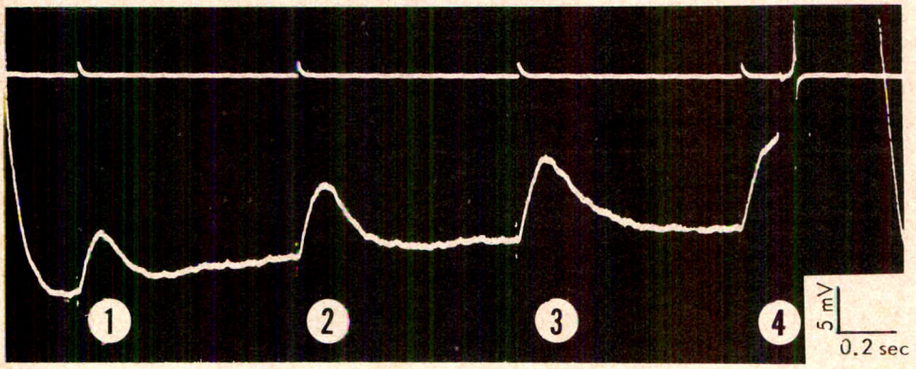

FIGURE 7. Experiment 2, position 9. Microelectrode recording of 4:1 block that occurred as a result of injury produced by prolonged exposure to the blocking current. The blocking current has been turned off. Numbers 1, 2, 3 and 4 represent successive electrotonic responses to artificial stimulation of a fiber showing slow depolarization. Response 4 is propagated and has an associated distal electrogram. See text for discussion.

component correlates well with the magnitude of delay.

Local responses: A considerable ambiguity exists in published reports concerning the nature and role in propagation of transmembrane potentials with low voltage and very slow upstroke velocities. A distinction is made between purely electrotonic potentials and graded or local responses. In our preparations, we frequently see evidence of local graded activity that distorts the voltage or contour of the electrotonic potential. This partial engagement of the active process, which does not progress to an all or nothing response, remains within the confines of passive transmission and has not been observed to be associated with active propagation. We object to the term "action potential" in reference to wave forms associated with block because "action" on the part of the fiber is usually not well defined.

Examination of the data obtained in our study reveals voltage and time variables that appear to be important determinants of the Wenckebach mechanism. Some of the electrophysiologic variables were not consistently observed in all cycles. Possible explanations for this, associated with the complex multifibered preparations, have been mentioned (see Results). The possibility of a spectrum of determinants operative in different cycles should also be considered.

Determinants of Wenckebach Mechanism

Changes in initial electrotonic potentials: An almost constant finding and the most direct determinant of Wenckebach periodicity was a progressive increase (more negative) in peak prepotential voltage with successive impulses in the cycle. The initial electrotonic potential that originated from the proximal boundary of the blocked zone became progressively less efficacious as a stimulus for the regenerative response at the distal block boundary with successive impulses of the cycle. A progressive voltage attenuation of the signal caused it to become progressively further removed from the threshold for stimulation of a regenerative response until the last impulse of the cycle failed to attain threshold, thus resulting in a nonconducted impulse. Phase 4 diastolic depolarization, relatively unaffected by the nonconducted electrotonic potential, allowed resetting for the next cycle by decreasing the base-line voltage toward threshold during the prolonged period between the last conducted impulse of the cycle and the first impulse of the next cycle. A progressive attenuation in rise time of the electrotonic potential resulted in a progressive delay of stimulation for the regenerative response at the distal block boundary with successive impulses of the cycle.

These observed changes in the initial electrotonic potentials resulted from two factors. The first was related to a progressive increase (more negative) in minimal diastolic voltage with successive impulses of the Wenckebach cycle. The base-line voltage level from which the transmitted electrotonic potential originated became further removed from threshold with successive impulses. This was an almost constantly recorded observation in all preparations and is apparent in Figures 4B and 5B. The second factor was a frequently observed progressive decrease in the onset to peak prepotential voltage occurring with successive impulses of the cycle. This decrease in absolute voltage of the electrotonic potential was secondary to the described increase in minimal diastolic voltage and was related to the voltage dependence of membrane resistance. An increase in membrane resistance associated with slow phase 4 diastolic depolarization was demonstrated in Purkinje fibers by Weidman.[19,24] Furthermore, the diastolic depolarization was not accompanied by significant changes in threshold potential so that later in diastole less stimulating current was required to initiate an all or nothing response.[24]

Figure 7 demonstrates this voltage dependence in an example of 4:1 block. Examination of the tracing reveals some slow depolarization. Superimposed are electrotonic potentials 1, 2, 3 and 4 in response to artificial stimulation. As the voltage decreases because of slow depolarization, the onset to peak voltage of the nonconducted electrotonic potentials becomes progressively greater. Finally, after three failures to elicit a propagated response, the fourth stimulus is associated with an electrotonic component sufficient to elicit a regenerative response that activates the distal tissue, as indicated by the electrogram in the top tracing.

The observed voltage changes of the onset to peak prepotential voltage during Wenckebach periods were the reverse of those seen in Figure 7. As the electrotonic potential originated from a greater (more negative) voltage, a decrease in membrane resistance resulted in a decreased fiber space constant that caused greater distance attenuation of the signal.

These phenomena are somewhat similar to those observed in 2:1 block,[3] in which the electrotonic potentials of alternate impulses fall below the threshold for stimulation, and are the opposite of those seen in 3:1 and higher grades of block, in which the electrotonic signals move progressively toward threshold with successive impulses resulting in a periodically conducted impulse (unpublished data).

Mechanisms producing alterations in the minimal diastolic voltage: A more basic problem related to the Wenckebach mechanism concerns the variables responsible for the observed progressive increase in minimal diastolic voltage. A constant finding in this regard was a marked increase in maximal as compared to minimal diastolic voltage associated with the first impulse of each cycle. Even in the presence of marked phase 4 depolarization this caused an increase in minimal diastolic voltage associated with the impulse of the second cycle compared to that of the first cycle. The fact that the electrotonic potential associated with the second cycle arose from a voltage markedly greater than that of the first cycle is the most likely explanation of the greatest increment of delay frequently observed in this portion of the cycle. A continued progressive increase in maximal diastolic voltage when observed with successive impulses of the cycle was thought to be an important determinant associated with progressive delay and, finally, nonconduction of the last impulse. This is seen in the three cycle recording of Figure 5A.

Another often observed finding which appeared to be an important determinant of minimal diastolic voltage was a progressive decrease in the diastolic interval (DI, Fig. 3) with successive impulses of the Wenckebach cycle. This change was usually due to a progressive encroachment upon the diastolic interval of each impulse by an increase in the total transmembrane potential duration (TMPD, Fig. 3) of the preceding impulse, which was in turn associated with an increased observed duration of the initial electrotonic component caused by a greater increment of delay. The effect of this change in the presence of slow phase 4 diastolic depolarization, which was always pronounced near the distal boundary of the blocked segment, would be to cause the transmitted electrotonic potential of the subsequent impulse to arise from a greater (more negative) diastolic voltage, thus, further removed from the threshold for stimulation of a regenerative response. This would cause a further increment of delay or nonconduction of an impulse. This mechanism is apparent in recording a of Figure 4A and in Figure 4B.

The mechanism for Wenckebach periodicity in terms of the transmembrane potential has not been adequately explained in published reports. We do not propose that the possibilities be restricted to a single mechanism for all cardiac tissues under all conditions of conduction disturbance; however, we have presented concepts derived from more extensive microelectrode exploration than has previously been performed. One might argue that block produced by an electrical blocking current may be unique. We do not believe so because identical wave forms were observed in segments of block produced by other methods, including localized iodine application used in our earliest studies and segmental block produced as an irreversible anodal effect from prolonged application of the blocking current.

Several factors should be emphasized concerning the interpretation of transmembrane potentials recorded in experimental block. High gain recording with our preparation indicated that the system is extremely sensitive to slight changes in voltage. Differences in the range of 1 to 2 mv appeared to be an important determining factor in the increment of delay or nonconduction of an electrotonic potential. In addition, the recording site for optimal demonstration of variables involved in the mechanism is found at the functional distal boundary, which may include a limited group of fibers in a multifibered preparation.

We cannot completely exclude the possibility that some other mode of conduction is occurring in one of the fibers of the multifibered preparation and that we are recording artifactual data; however, the syncytial nature of the fibers and the fact that we have never observed such phenomena in extensive microelectrode exploration of blocked segments, including fibers at various depths, argue against it.

Clinical implication: Although Wenckebach periodicity may occur clinically in the bundle branches,[25,26] the site of primary interest is in the junctional tissues proximal to the bundle of His in most cases.[18,27,28] We have no data specifically indicating that the mechanisms we have described are operative in the area of the A–V node; however, similar two component transmembrane wave forms have been recorded in the A–V node by many investigators,[7,10,15,16,29–34] thus suggesting that similarities in the mode of conduction under normal and abnormal conditions may exist.

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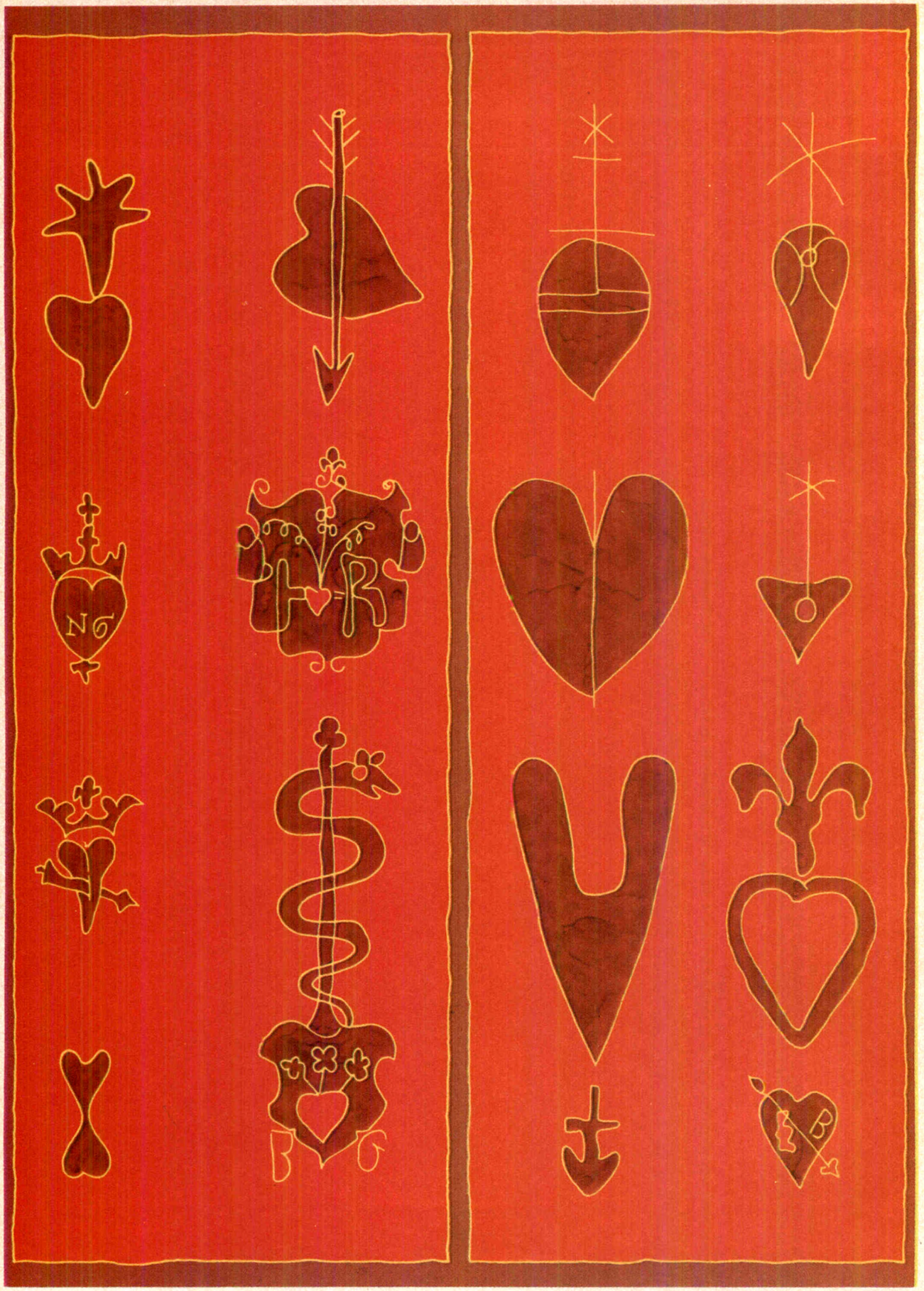

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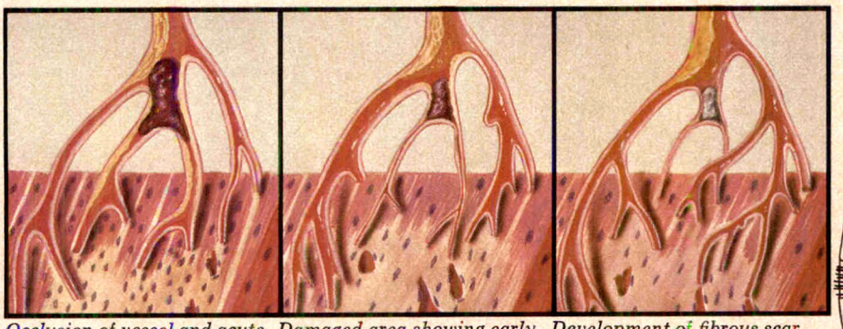

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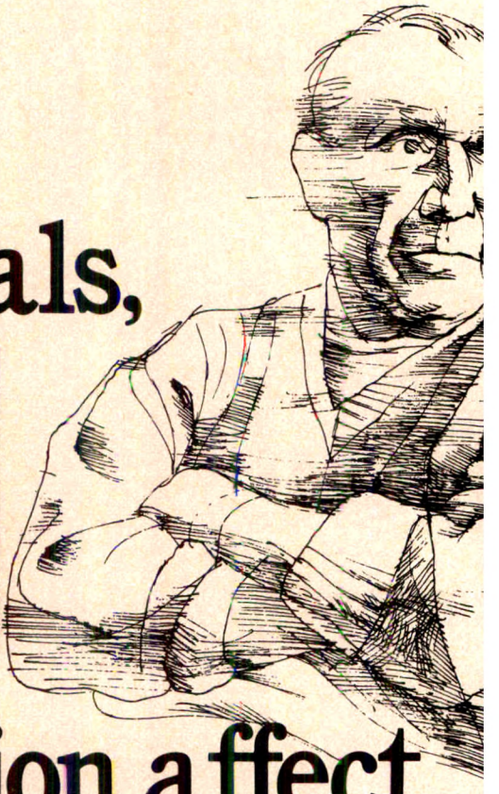
Damaged area showing early collateral vessel formation.

Development of fibrous scar and healing of infarcted area.



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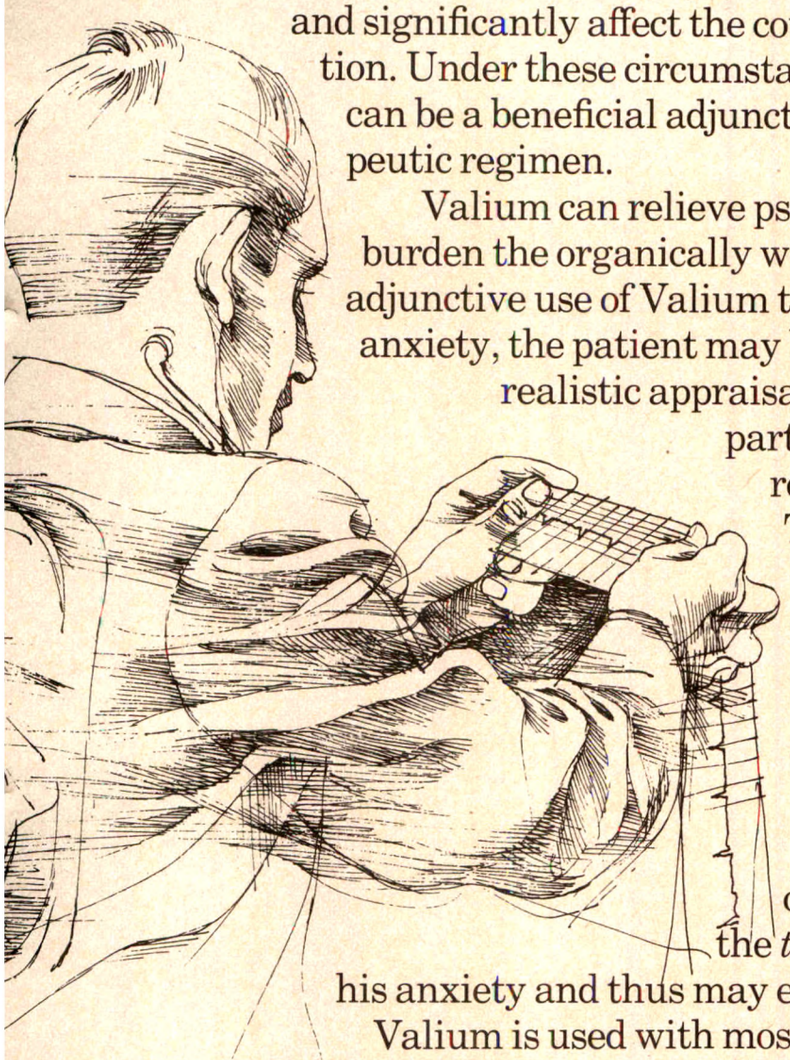

Valium can relieve psychic tension that may burden the organically weak heart. As a result of adjunctive use of Valium to relieve unwarranted anxiety, the patient may be able to arrive at a more realistic appraisal of his situation and participate more fully with his rehabilitation program.

Therapy should normally be continued until the patient's anxiety has been reduced to tolerable levels.

Since the cardiac patient may be particularly prone to tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *t.i.d.* schedule can relieve his anxiety and thus may encourage sleep.

Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticholinergics and antacids. The most commonly reported side effects have been drowsiness, fatigue and ataxia. Patients taking Valium should be cautioned against driving or operating dangerous machinery.

Valium®(diazepam)
2-mg, 5-mg, 10-mg tablets

when you consider it essential to keep the heart patient calm

Please turn page for a summary of product information.

When you consider it essential to keep the heart patient calm

- Valium (diazepam) can relieve psychic tension and anxiety that may burden the organically weak heart and interfere with the patient's course of rehabilitation.
- Valium works promptly in most patients. Significant improvement is usually noted during the first few days of therapy, although some patients may require more time to respond.
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- Valium has a wide margin of safety in the usual oral dosage range and generally does not significantly affect respiration or pulse.

Valium® (diazepam) 2-mg, 5-mg, 10-mg tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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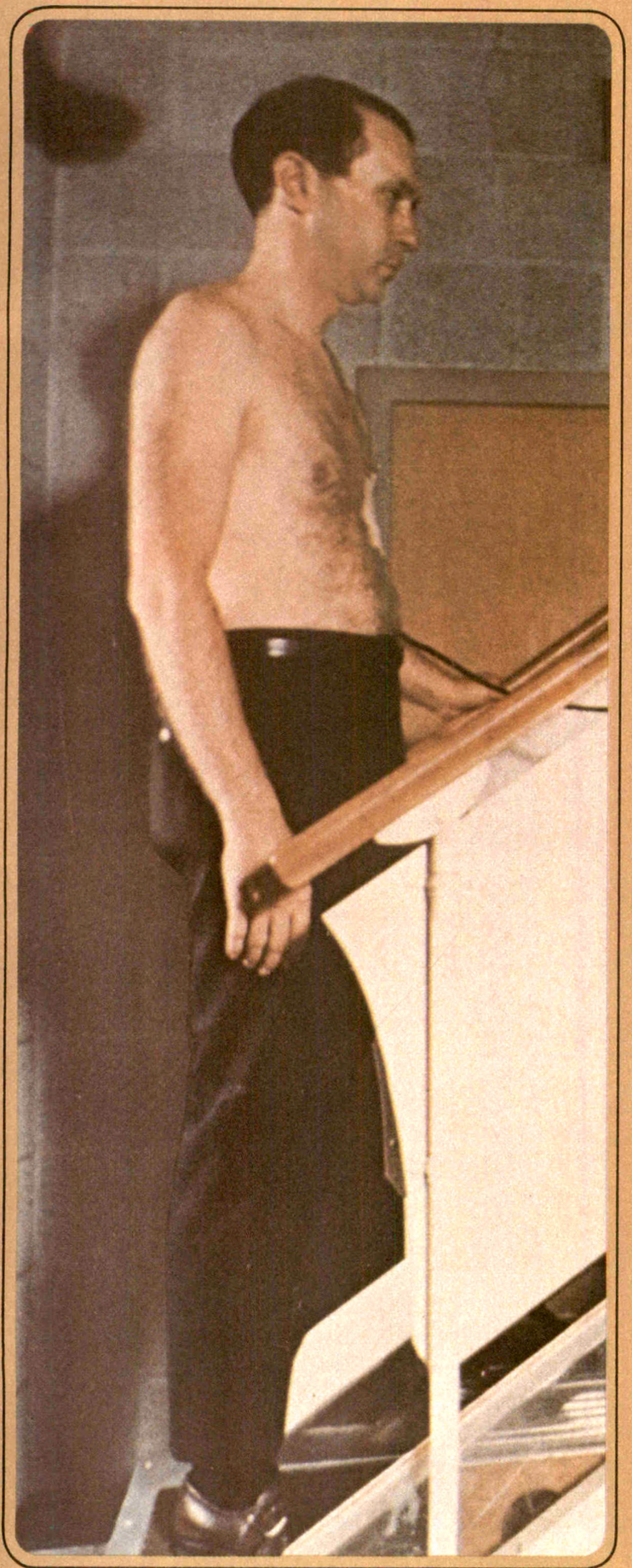

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SIDE EFFECTS: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound.

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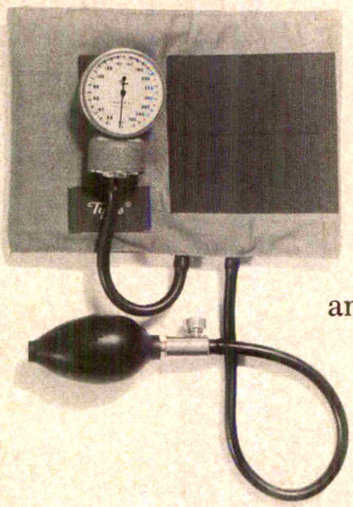

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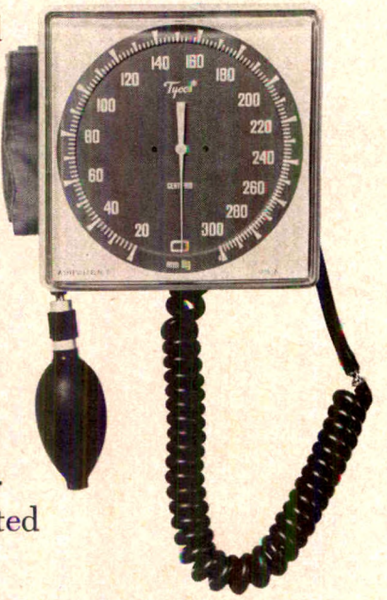

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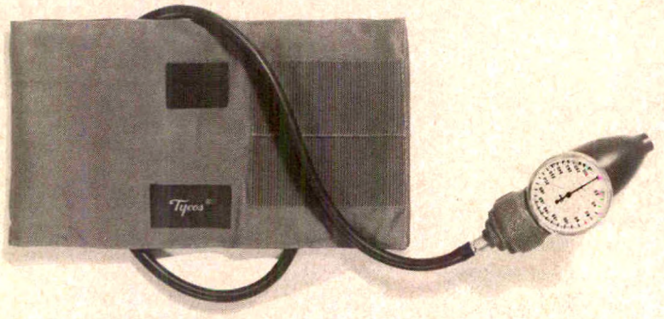

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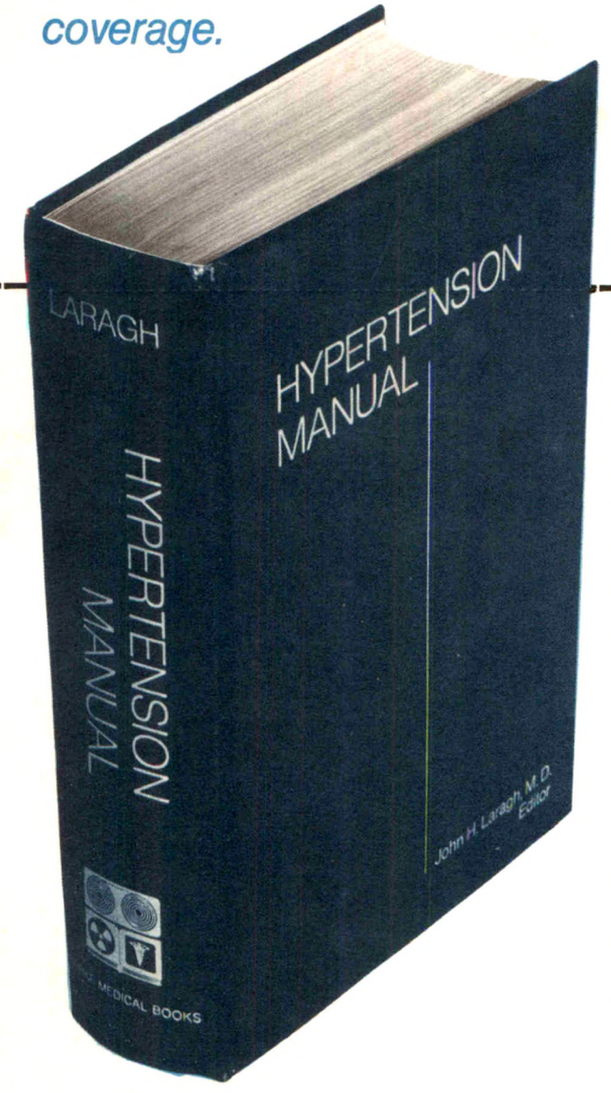

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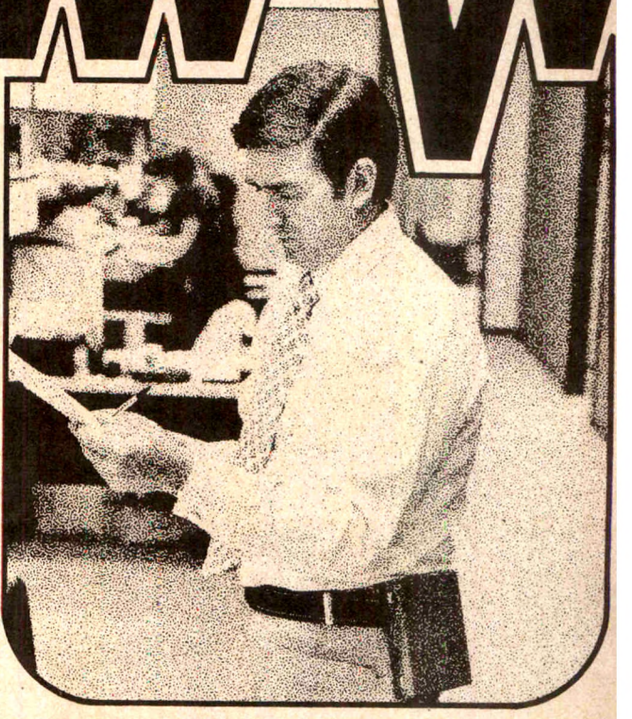

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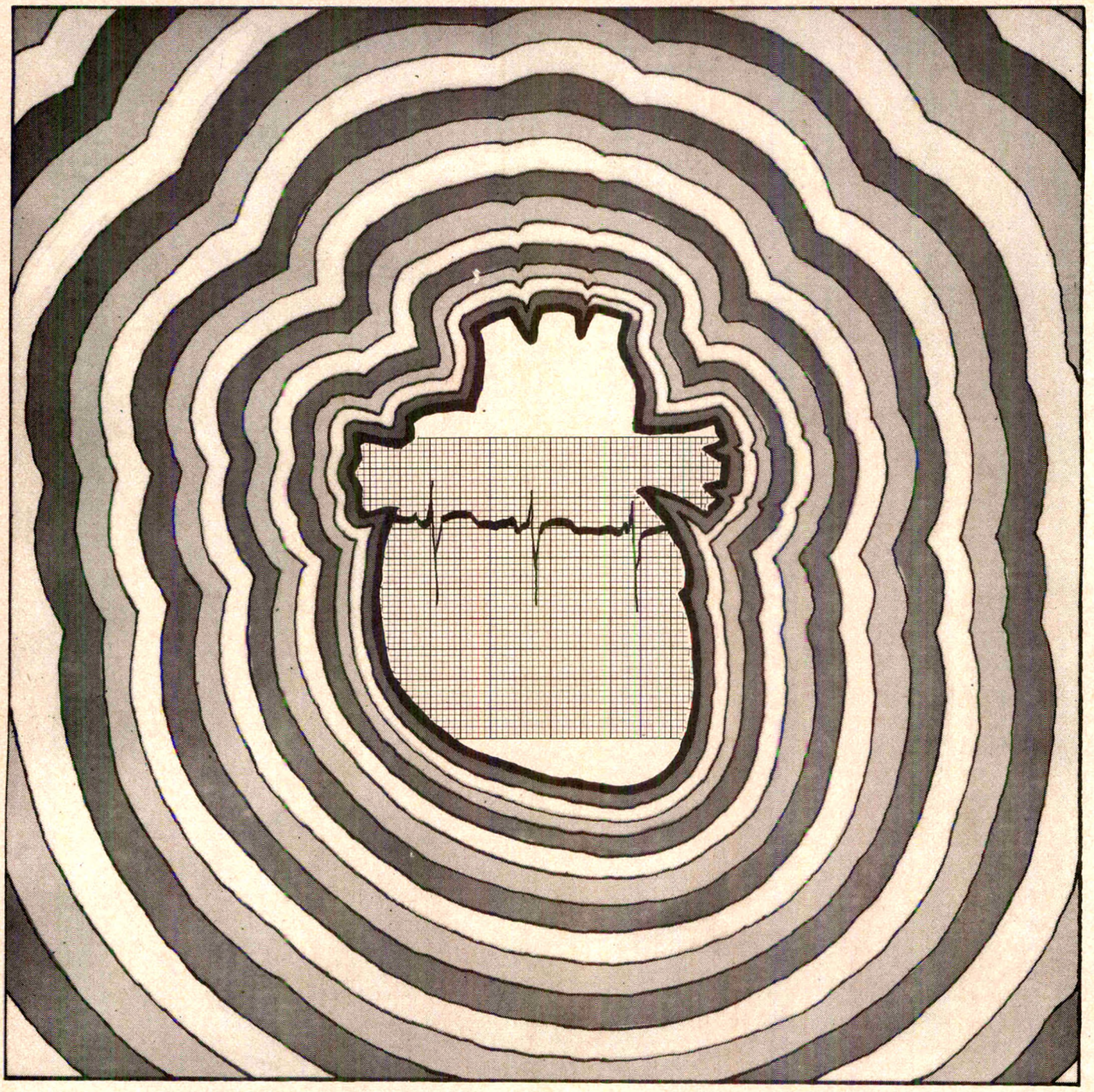

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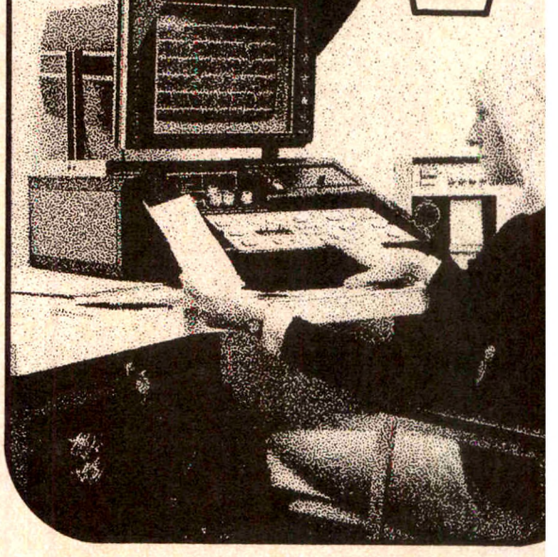

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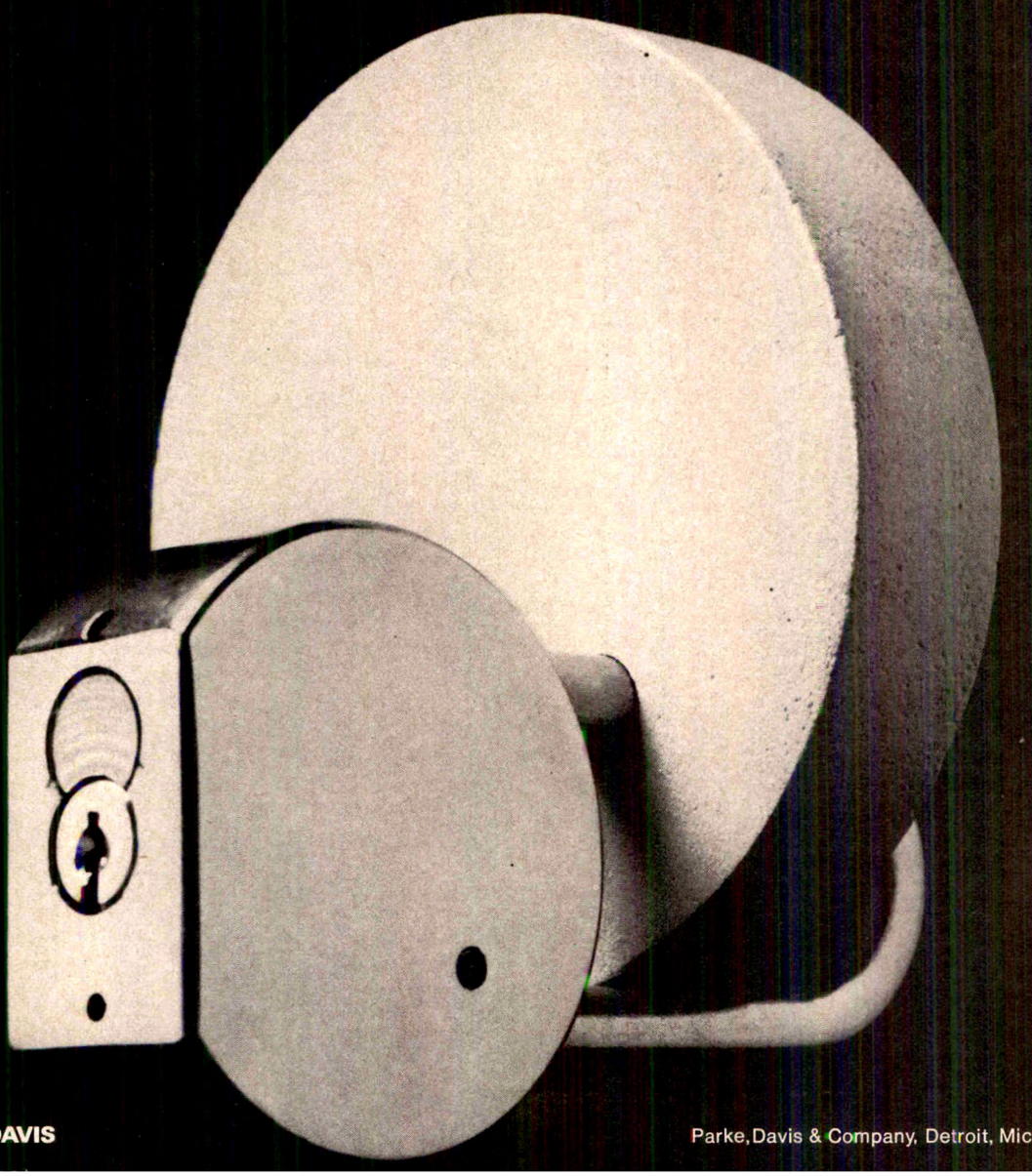

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Detection of Ventricular Arrhythmias in Real-Time with a Portable Analog Computer

DAVID S. CANNOM, MD
DONALD C. HARRISON, MD, FACC

Stanford, California

Recent studies on the occurrence of sudden death emphasize that many patients have ventricular premature contractions as prodromes of lethal arrhyhmias. A portable, 6 ounce analog computer has been developed to detect tachycardias (heart rate 150 to 190 beats/min), bradycardias (heart rate less than 50 beats/min) and ventricular premature contractions. When preset limits are exceeded, acoustic warnings are sounded, and the patient may transmit his electrocardiogram by telephone, without additional equipment, to a receiving device that graphically reproduces the electrocardiogram in real-time. Hospital studies in 26 ambulatory patients with a variety of arrhythmias have been completed. Tachycardias and bradycardias were detected in every instance during 30 observation periods in six patients. Reproducible warnings were triggered in 19 of the 20 patients with ventricular premature contractions of various configurations during each of 5 observation periods (100 observations). In one patient, the electrical vector of the ventricular premature contraction closely resembled the normal QRS vector and was not detected. Appropriate electrode placement is essential to avoid initial Q waves and to maximize the difference between the vector of ventricular premature contraction and that of the normal QRS complex. No false positive acoustic alarms were sounded. Our results demonstrate that it is possible to detect ventricular premature contractions readily and reproducibly in ambulatory patients. Use of this detector may permit large scale monitoring of patients with a high risk of sudden death.

During the 1960's the establishment of coronary care units for the treatment of serious ventricular arrhythmias considered premonitory of cardiac arrest significantly reduced the in-hospital mortality rate of acute myocardial infarction.[1] It seems likely that further reduction of the in-hospital mortality rate will be limited, since most of these deaths are due to massive myocardial necrosis with severe pump failure.

A major reduction in the mortality rate of myocardial infarction may be possible in the group of patients who die outside the hospital. Recent studies have shown that 50 to 70 percent of all deaths from infarction occur in nonhospitalized patients.[2] Many of these occur suddenly, and pathologic examination of the heart reveals extensive coronary artery disease and myocardial ischemia but no evidence of massive myocardial necrosis.[3] It is probable that these deaths are caused by ventricular arrhythmia, since many occur instantaneously. In many patients, perhaps 30 to 35 percent, sudden death may be the first clinical sign of coronary artery disease.[2] There are several indications that these patients may be identified as being at high risk for sudden death: (1) As many as 23 to 33 percent of patients dying suddenly have visited their physician within 2 weeks of death.[4,5] (2) Ventricular arrhythmias occur as premonitory signs of cardiac arrest in

From the Cardiology Division, Stanford University School of Medicine, Stanford, Calif. This work was supported in part by Grants HE-5866 and HE-5709 from the National Institutes of Health, Bethesda, Md. Manuscript accepted July 5, 1973.

Address for reprints: Donald C. Harrison, MD, Cardiology Division, Stanford University School of Medicine, Stanford, Calif. 94305.

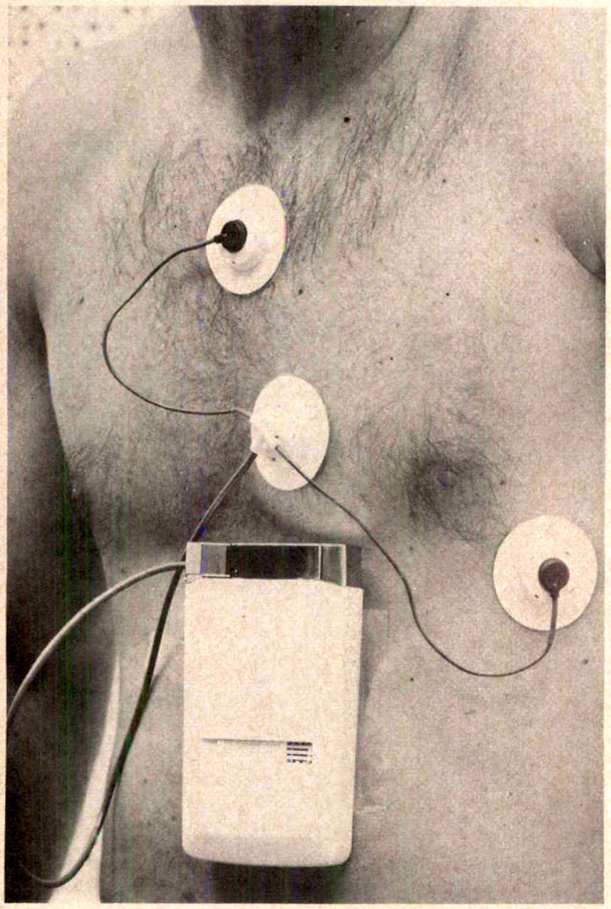

FIGURE 1. Analog computer attached to a patient during a study, showing the R wave-sensing electrodes positioned in the regions most commonly used, one applied apically and one midsternally. A common electrode is placed between these two, and the electrodes are connected by a cable to the computer.

outpatients who have been monitored.[6] (3) Patients with prior episodes of coronary artery disease are at higher risk for sudden death than the general population.[2]

By detecting prelethal arrhythmias that herald sudden death it may be possible to identify and treat patients at high risk. Accordingly, we have evaluated a device that permits continuous real-time monitoring of cardiac rhythm and the initiation of alarms when preset conditions are exceeded. Such a device will allow monitoring of outpatients who are suspected to be at high risk for sudden death.

This study outlines our preliminary experience with a small analog computer attached to the patient by electrodes. The instrument detects tachycardias, bradycardias and ventricular ectopic beats. When preset limits are exceeded, acoustic alarms are sounded and the patient can transmit his electrocardiogram in real-time by ordinary telephone to a receiving unit, where the electrocardiogram can be printed on a strip chart and analyzed. This preliminary study describes the use of this device in detecting arrhythmias in a controlled in-hospital setting. Ongoing studies are evaluating its usefulness in ambulatory hospital patients and outpatients.

Materials and Methods

Twenty-six patients hospitalized in the Cardiology Service at Stanford University Hospital were selected for study because their standard electrocardiograms showed either premature ventricular contractions, supraventricular tachycardias or sinus bradycardias. An additional 14 patients with electrocardiograms whose QRS complex had an unusual configuration, such as a bundle branch block pattern or marked ST–T wave changes, were studied to determine the potential for false positive alarms caused by such electrocardiographic changes when the analog computer detector was used.

The Instrument

The instrument evaluated in these experiments (VIDA, Cardiodynamics-Vida Medical Systems, Dublin, Calif.) is shown in Figure 1. It is a 6 ounce analog computer that can be operated for 30 days without replacement of its self-contained battery. It looks like a small transistor radio and can be worn in a coat pocket, special belt holder or shirt pocket. The computer contains electronic circuitry that performs the following primary functions: (1) electrocardiographic signal amplification; (2) nonlinear analog wave form processing; (3) ventricular ectopic beat identification; (4) ectopic interval evaluation; and (5) signaling of audio alarms to the patient when preset limits are exceeded.

The electrical signal from the electrodes is amplified to an appropriate level by the input amplifier. This signal is processed by a nonlinear circuit that is sensitive to the sharpness of initial slope of ectopic beats but ignores normal QRS configurations. When the processed signal exceeds a specific value, a binary signal is generated to indicate that an ectopic beat is occurring. If two such occurrences are separated by less than a preprogrammed interval, the unit produces an 8 second audible tone. This signals the patient that the criteria for ectopic activity established by the physician have been exceeded and, depending upon the clinical situation, specific actions should be taken.

Several secondary functions are performed by the instrument: (1) detection of tachycardia; (2) detection of bradycardia; and (3) telephone transmission of an audio signal that can be converted to an electrocardiogram.

The rate at which normal QRS complexes occur is converted to a voltage and compared against preprogrammed limits. If the voltage exceeds the limit for tachycardia (set between 150 and 190 beats/min) or falls short of the limit for bradycardia (less than 50 beats/min), the audio tone sounds a different alarm, a short, high-pitched "beep," corresponding to each heart beat.

The instrument also has the capacity to transmit the electrocardiogram wave form in real-time to a central receiving point with use of regular telephone service. To transmit the low frequency electrocardiographic signal over a telephone line intended for voice frequencies, an FM (frequency modulation) modulator is used. The analog computer emits a constant frequency tone (about 2,000 cycles/sec) when the electrocardiographic wave form is at its base-line value. This tone varies in pitch as the electrocardiogram varies from its base line: An upward or positive variation of the electrocardiogram results in a higher pitch, and a downward variation results in a lower pitch.

At the receiving station, a complementary instrument converts this varying period signal back to an ordinary low frequency electrocardiogram and records it on a strip chart

recorder. The overall system maintains the 0.05 to 100 Hz standard suggested by the American Heart Association for recording of electrocardiograms.

Method of Study

Each patient was studied in a similar fashion. Since the instrument recognizes only pure or predominant R waves, irrespective of their precise configuration, the position for placing the electrodes on the chest is important. The patient lay supine and his precordium was initially explored with use of two suction cups attached to the right and left arm leads of a standard electrocardiogram until bipolar lead I showed a predominant R wave. An initial Q wave or large S wave, as part of an RS complex, was always eliminated by continued precordial mapping. Typically, placement of one electrode apically and one midsternally was the most favorable electrode position.

The skin in the area was shaved, and commercial electrodes (NDM disposable electrodes, Bionetics, Inc., Dayton, Ohio) were applied to the sites previously shown to provide the largest R wave. The electrodes were attached to the computer by a short insulated wire (Fig. 1).

Each patient was monitored simultaneously by either an electrocardiogram or an oscilloscope attached to a separate pair of electrodes placed near those of the computer. The study in each patient was personally observed by one of us.

Five different computer units were used in succession during the study of each patient. Each patient studied with a single unit was considered to comprise an individual observation, so that each patient studied with five different units in succession comprised five observations. Comparison between the response of the unit and the simultaneously recorded electrocardiogram forms the basis of our results. In each case, when an alarm sounded, telephone transmission to the receiving unit was made by the patient to test this modality of the device.

Results

Six patients with tachycardias or bradycardias were studied. In each case, the unit responded with the appropriate repetitive acoustic signal when the rate was either faster than 150 or slower than 50 beats/min, the limits chosen for this study. Figure 2 shows an example of the unit's response to a tachycardia and a bradycardia. Thus, for this group of patients, there were 30 accurate observations, with no false positive or false negative alarms.

A total of 20 consecutive patients with more than five ventricular premature contractions per minute were studied. Although any number of ventricular premature contractions per minute could have been chosen, five per minute was the criterion selected for this study. An additional 14 patients with bundle branch block configurations, deeply depressed S–T segments or inverted T waves were studied to determine whether such changes would affect the unit's capability to detect ventricular premature contractions. No variations in QRS or ST–T configurations triggered false positive alarms in these 14 patients.

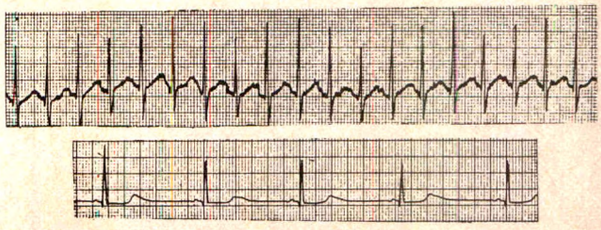

FIGURE 2. Examples of a tachycardia **(above)** and bradycardia **(below)** detected by the device, showing strip-chart printouts of the arrhythmias as transmitted over ordinary telephone lines. A short, high-pitched acoustic "beep" sounded with the occurrence of each QRS complex, alerting the patient to an arrhythmia. Paper speed 25 mm/sec.

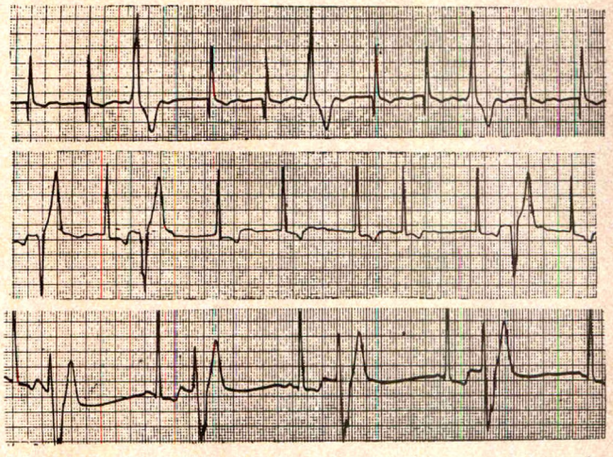

FIGURE 3. Three panels showing representative premature ventricular contraction configurations detected by the computer. If two premature contractions occurred within 12 seconds, an 8 second acoustic alarm sounded and continued to sound if the arrhythmia was repetitive. Paper speed 25 mm/sec.

In 19 of the 20 patients with ventricular premature contractions, the device correctly identified the contraction if two occurred within 12 seconds of each other (that is, at a rate of five per minute). The acoustic alarm, lasting 8 seconds, sounded each time two ventricular premature contractions occurred in this interval; it continued to sound if these contractions were frequent or persistent. Examples of the various wave forms detected are shown in Figure 3. Each of these arrhythmias was tested with all five units, and there were no differences in response of the units studied. Although many of the alarms were repetitive in these 19 patients, in the 95 observations

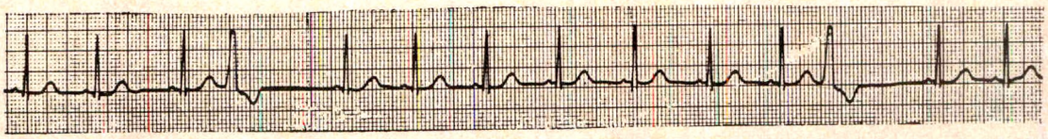

FIGURE 4. Transmitted recording of the patient whose premature ventricular contractions were not detected by the device. The initial vector of the premature contraction is similar to that of the normal sinus QRS complex. Paper speed 25 mm/sec.

made, there were no false positive or false negative alarms.

In one patient, ventricular premature contractions (Fig. 4) were not detected by any of the five units. The probable explanation for this failure is that the slope of the initial R wave of these contractions was very similar to the slope of the sinus R waves. In this patient, it was not possible to change electrode position so that the vector of the ventricular premature contractions differed significantly from the sinus QRS vector. These five observations represent the only false negative results in the study. It should be emphasized, however, that all patients had preexisting ventricular premature contractions, so that appropriate electrode placement on the chest could be made to detect the arrhythmia.

Discussion

The 26 patients studied in this carefully controlled manner to evaluate the sensitivity and specificity of the design model arrhythmia detector demonstrate the capabilities of this analog computer. The behavior of the five units in detecting tachycardias and bradycardias was uniformly satisfactory. Premature ventricular contractions of various configurations were successfully detected in 19 of 20 patients. The failure to detect ventricular premature contractions in one patient (Fig. 4) was probably related to the logic of the computer, which requires recognition of a change in the slope of the initial R wave of the QRS complex. The slope of the R wave of this patient's ventricular premature contractions was virtually identical to that of the base-line QRS complex, representing those ectopic beats that are beyond the capability of this unit to recognize and detect.

We do not expect the capability of the device to detect premature ventricular contractions to approach 95 percent in a randomly selected outpatient population. Knowledge of the vector of the ventricular premature beats in our controlled population permitted electrode placement that enhanced the arrhythmia detection capabilities of the device in our study. In randomly selected patients without previously existing ectopic beats of known vector, the frequency of failure to detect ventricular premature contractions would be greater. Studies are currently underway to document this point; however, the circuitry of this equipment is designed to avoid a high prevalence of false positive signals.

The transmission capability of the unit was tested in each case. Patients had no difficulty with the mechanics of telephone transmission. The electrocardiograms graphically reproduced by the receiving device during telephone transmission are of high quality, as can be appreciated from the illustrations.

Clinical implications: Our studies suggest that this device has important implications for the patient who has, or who can be expected to have, arrhythmias. A unit potentially suitable for outpatient use is now available for monitoring arrhythmias in real-time and alerting the patient and his physician to arrhythmias when they occur. The unit will permit assessment of therapy and treatment of the patients while they are experiencing the arrhythmia. The effect of such real-time monitoring of patients at high risk for sudden death remains unknown. Clearly, the study of such patients by detecting premonitory lethal rhythms is now possible using the analog computer described. A unit of this kind would appear ideal for surveying these patients clinically and for research purposes.

Our studies were performed under carefully controlled circumstances to evaluate the capabilities of the computer itself. Careful mapping of the chest for the vector of ventricular premature contractions is essential; good electrode contact and maintenance is necessary; educating the patient to understand the alarms is required; and psychological support for the patient using the system is mandatory. Our findings suggest that controlled outpatient studies should now be attempted both to define the problems of long-term electode placement and patient acceptance and tolerance of the concept of continuous monitoring and to establish mechanisms for telephone transmission to a coronary care unit or central hospital facility. Resolution of these potential problems must be achieved before widespread outpatient use of this device can be undertaken.

Acknowledgment

We gratefully acknowledge the technical assistance of Miss Mary Ann Austin in the performance of these studies.

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Ventricular Septal Defect with Increased Pulmonary Vascular Resistance

Late Results of Surgical Closure

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The fate of 57 children who underwent surgical closure of ventricular septal defect in the presence of increased pulmonary vascular resistance was analyzed. Eighteen (32 percent) died at or immediately after operation. Seven late deaths, due to the Eisenmenger syndrome, occurred 1 to 7 years after operation. Follow-up studies, including cardiac catheterization, were performed in 25 survivors, 1 to 11 years (mean 5 years) after operation. In patients operated on after age 2 years, the degree of preoperative elevation of pulmonary vascular resistance largely determined the prognosis: The condition of patients with mild elevation (pulmonary vascular resistance less than one third the systemic level) returned to normal after operation, with one exception. Patients with more severe elevation (pulmonary vascular resistance more than one third the systemic level) most often showed progressive pulmonary vascular disease; the condition of a few remained unchanged and that of only one returned to normal after operation.

Operative mortality rate was high in children with elevated pulmonary vascular resistance during the second year of life who were operated on before age 2 years, but pulmonary vascular resistance returned to normal in the three survivors. When pulmonary vascular resistance was increased in the first year of life, it generally decreased spontaneously (independently of operation); the early increase in these cases is believed to represent delayed maturation of the pulmonary vascular bed rather than pulmonary vascular disease.

The overall results of surgery in ventricular septal defect associated with a high level of pulmonary vascular resistance are unfavorable and call for interruption of the natural history before significant pulmonary vascular obstructive changes have taken place; this can be achieved by surgical closure before age 2 years or pulmonary artery banding in infancy.

Pulmonary vascular disease is a serious complication in a significant number of patients with a large ventricular septal defect.[1–5] It is generally agreed that the advanced stage with right to left or bidirectional shunting, known as the Eisenmenger syndrome, constitutes a contraindication to surgery. However, controversy exists about the fate of patients whose ventricular septal defect is closed in the presence of a mild or moderate increase in pulmonary vascular resistance. Although some investigators[6–9] have indicated a marked postoperative reduction in pulmonary vascular resistance, to normal in many cases, others[10,11] have found little change. Concern has been repeatedly expressed that pulmonary vascular disease may progress further after closure of the defect. Although severely increased pulmonary vascular

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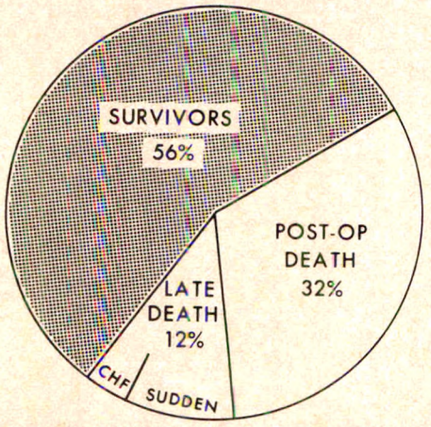

FIGURE 1. Fate of 57 patients operated on for ventricular septal defect and pulmonary vascular disease, including early postoperative and late deaths. Late fatalities were due more often to sudden death (five cases) than to congestive heart failure (CHF) (two cases).

resistance has long been considered a contraindication to surgery in this hospital, 57 patients with mild to moderately severe elevation of resistance underwent surgical repair of ventricular septal defect between 1955 and 1971. In this paper, we present their postoperative course, including results of long-term follow-up catheterization studies in the survivors.

Material and Methods

Patients were selected for study whose pulmonary vascular resistance was more than 25 percent of the systemic vascular resistance and in excess of 400 dynes sec cm^{-5} per m^2. At operation their ages ranged from 11 months to 17 years (mean 4.8 years).

Postoperative catheterization was performed in 25 of the survivors and repeated in 2. All catheterization studies were carried out with the patient under light sedation induced by a mixture of meperidine, 25 mg, chlorpromazine, 6.25 mg, and promethazine, 6.25 mg/ml (0.1 ml/kg). Pressures were recorded on an Electronics for Medicine DR8 recorder and transmitted from Statham transducers. Oxygen content of venous, systemic arterial and pulmonary arterial blood was measured using a Waters cuvette oximeter.

Flow measurements were calculated[2] using an assumed value for oxygen consumption of 180 cc/min per m^2. Because this procedure may introduce an error of unknown magnitude into calculations of absolute flow and resistance levels, we have elected to report our results in terms of flow ratios (pulmonary blood flow over systemic blood flow) and resistance ratios (total pulmonary vascular resistance over systemic vascular resistance) expressed as a percentage. Both of these measurements are independent of oxygen consumption, and we believe that they are the most reliable in a primarily retrospective study of this kind. Patients with a residual ventricular septal defect were included in the study only when the oxygen saturation data indicated an insignificant left to right shunt (pulmonary/systemic flow ratio between 1 and 1.5), and the pulmonary vascular resistance had returned to normal.

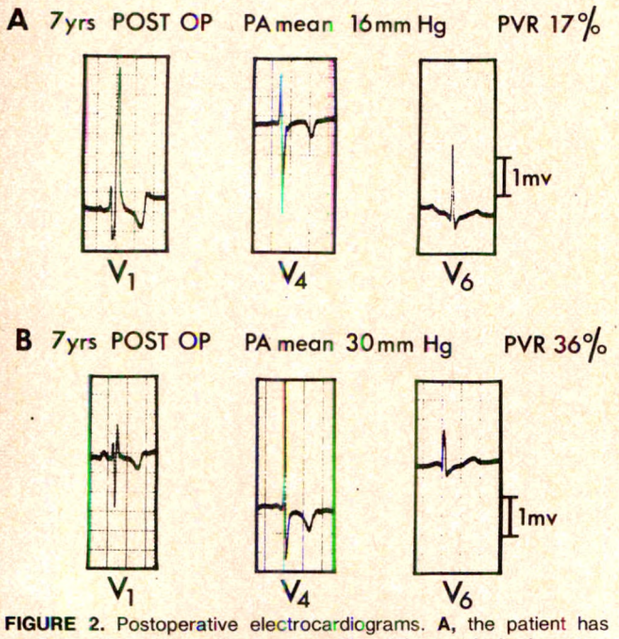

FIGURE 2. Postoperative electrocardiograms. **A,** the patient has electrocardiographic evidence suggesting right ventricular hypertrophy, although normal pulmonary arterial (PA) pressure and resistance (PVR) values were found. In another patient **(B),** no signs of right ventricular hypertrophy exist despite moderately elevated pulmonary arterial pressure and resistance values.

Results

Mortality

There was a high operative mortality rate (Fig. 1). Twelve of the 18 postoperative deaths occurred in patients who were operated on in the first, second or third year of life for increasing pulmonary vascular resistance. In many of these cases the operation had been performed between 1955 and 1961. There were, in addition, seven instances of late death (12 percent). These occurred 1 to 7 years postoperatively and were all due to the Eisenmenger syndrome; the patients' ages at death ranged from 7 to 16 years. Sudden death was characteristic of this subgroup (five of seven); one occurred during right ventricular angiography, the other four while the children were at school or at play. The remaining two children died with congestive heart failure. Postmortem examination, performed in 17 patients, revealed grade II to IV pulmonary vascular changes according to the classification of Heath and Edwards.[12] There were 32 long-term survivors (56 percent of the total group).

Follow-Up Study

In assessing the state of the pulmonary vascular bed after operation, one must rely heavily on the hemodynamic data. Although advanced pulmonary vascular disease can be diagnosed clinically by use of auscultation and chest roentgenogram, we have found it difficult to recognize persistence of mildly or moderately increased pulmonary vascular resistance without a catheterization study. The most sensitive preoperative indicator of pulmonary hypertension, the electrocardiogram, can be misleading postoperatively (Fig. 2). Very tall R waves in lead V_1 may be seen in the presence of normal pulmonary arterial

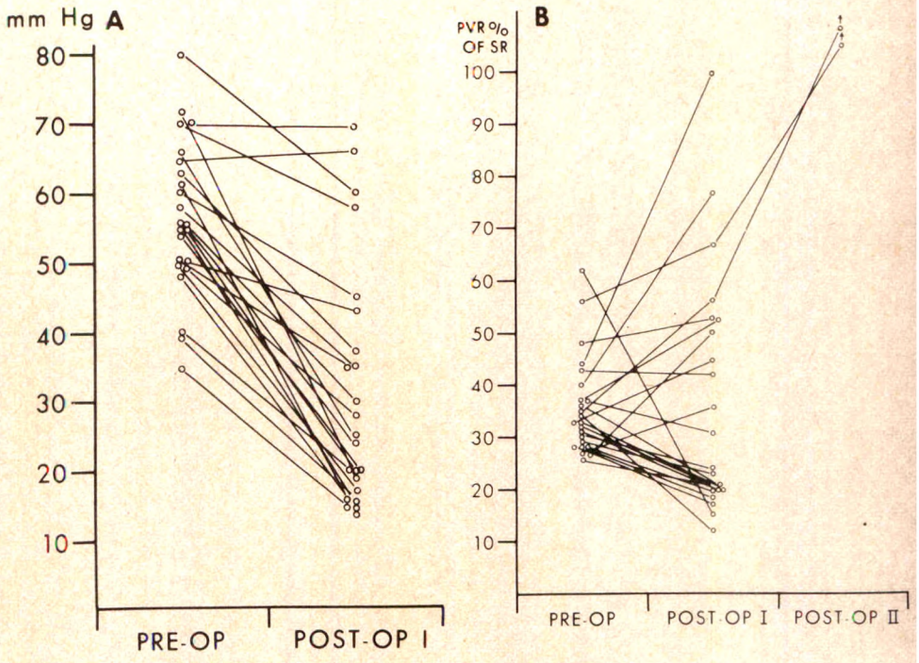

FIGURE 3. Pre- and postoperative values for pulmonary arterial pressure **(A)** and resistance **(B).** There is a tendency toward decreasing pulmonary arterial pressure, but resistance values show a wide scatter. Post-op I and II = first and second postoperative catheter studies, respectively; pre-op = preoperative data; pulmonary vascular resistance is presented as a percentage of systemic resistance (PVR % OF SR).

pressure; more rarely, patients with increased pulmonary vascular resistance may have no evidence of right ventricular hypertrophy on the electrocardiogram. This phenomenon may be caused by the postoperative intraventricular conduction disturbance; it has been suggested[13] that, in some cases, persistent signs of right ventricular hypertrophy indicate abnormal reactivity of the pulmonary vascular bed.

Hemodynamic Data

Twenty-five of the survivors were submitted to cardiac catheterization 1 to 11 years after operation, whether or not persistent pulmonary hypertension was suspected on clinical grounds. Four patients had a small residual ventricular septal defect that was hemodynamically insignificant (pulmonary to systemic flow ratio between 1.0 and 1.5). In the 21 other patients the defect was completely closed.

As shown in Figure 3A, pulmonary arterial pressure was reduced to some degree in all but two patients, although seldom to normal values. Because all patients had a sizable left to right shunt before operation, this reduction can be expected to occur independently of any change in pulmonary vascular resistance simply because of decreased pulmonary blood flow. Indeed, pulmonary vascular resistance did not show a uniform tendency to decrease (Fig. 3B). A large scatter in resistance values was found at follow-up catheterization: In some patients, values had returned to normal or near normal levels, whereas in others they had remained unchanged or had definitely increased, in some instances to systemic levels or higher.

The patient population was classified according to age and degree of preoperative elevation of pulmonary vascular resistance. Findings in the three main groups follow.

Patients operated on after age 2 years: In this group of patients, the degree of elevation of pulmonary vascular resistance before operation seemed to be the critical factor determining the prognosis. Figure 4A shows the outcome in patients with mild to moderate elevation, as defined by a value for pulmonary vascular resistance between one fourth and one third the systemic value. Of the eight patients in this group, six manifested a return to normal levels after operation. One showed a mild increase 7 years after operation, but he is well clinically 11 years postoperatively, and another catheterization study has not been considered warranted. The only patient in this subgroup with a clear-cut increase in pulmonary vascular resistance suggesting progressive pulmonary vascular disease happens to be our oldest patient, who was operated on at age 17 years.

Data from patients with a moderately severe increase in pulmonary vascular resistance, defined as a resistance value more than one third the systemic value (Fig. 4B), suggest that the prognosis in this subgroup is much worse. The level of pulmonary vascular resistance returned to normal in only one patient, and this subject had a preoperative value close to one third the systemic value. The other patients either had no significant changes in resistance or, more often, showed clear-cut progression of pulmonary vascular disease. Seven patients demonstrated clinical features of the Eisenmenger syndrome: loud pulmonic second sound, pulmonary regurgitation and signs of pulmonary vascular disease on the chest roentgenogram. Two of these patients underwent a second postoperative catheterization and were found

to have above systemic levels of pulmonary vascular resistance, with a value for peak pulmonary arterial pressure of 180 mm Hg in one and twice the systemic value in the other. Three patients in this subgroup were among those who experienced a late death.

Two additional children had progressive pulmonary vascular disease after operation, one of whom has died. They are not included in the graph because they did not have preoperative catheterization studies. However, both had clear-cut clinical evidence of increased pulmonary vascular resistance before surgery and were operated on for this reason, in the third and fourth years of life, respectively. Both were found to have pulmonary vascular resistance at systemic level at catheterization, 2 and 5 years postoperatively.

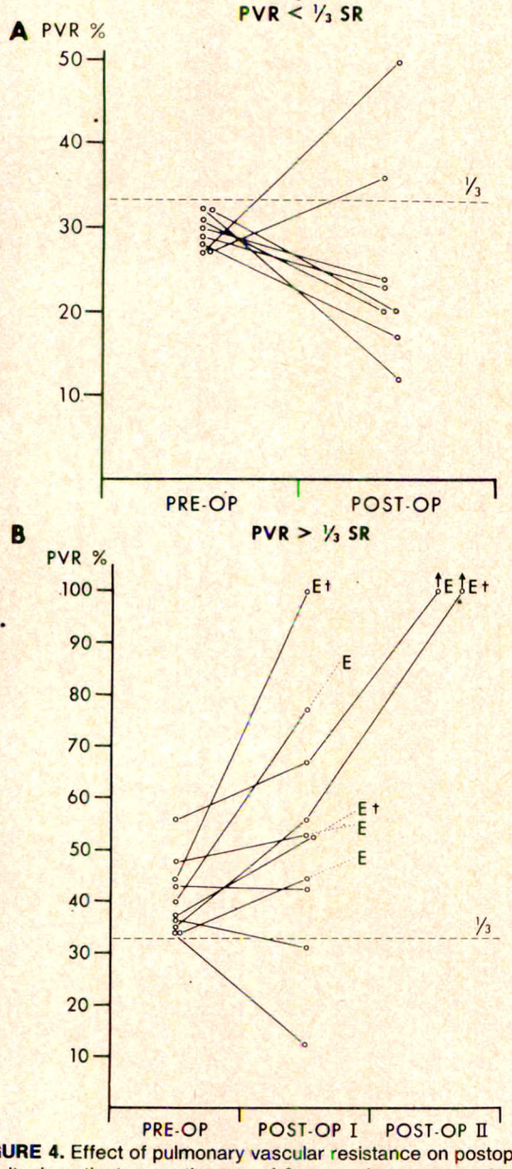

FIGURE 4. Effect of pulmonary vascular resistance on postoperative results. In patients over the age of 2 years, the postoperative evolution is related to the degree of preoperative elevation of pulmonary vascular resistance (PVR). The prognosis is favorable if this value is less than one third the systemic value (SR) **(A).** Progressive pulmonary vascular disease most often occurs when the preoperative level of pulmonary vascular resistance is more than one third the systemic level **(B).** E = clinical evidence of Eisenmenger syndrome.

Patients operated on before age 2 years: Nine patients who had increased pulmonary vascular resistance in the second year of life were operated on before age 2 years. Figure 5A shows their preoperative and postoperative course plotted against the normal maturation line for pulmonary vascular resistance.

All those whose catheterization had been performed in infancy had at that time reduced pulmonary vascular resistance, well below the normal maturation level, but all had a high level of pulmonary blood flow, more than three times the systemic level. When their pulmonary vascular resistance increased markedly in the second year of life, surgical closure of the ventricular septal defect was attempted. Six did not survive the operation; all were found at autopsy to have intimal changes in their pulmonary arterioles (grade II, some even grade III). All three survivors had normal or near normal resistance at follow-up catheterization, although one had moderately severe elevation of pulmonary vascular resistance preoperatively.

Patients with a high level of pulmonary vascular resistance in infancy operated on later: Figure 5B shows the course of five patients with a high level of pulmonary vascular resistance in the first year of life. Three of these patients are not included in the group of 57 who form the basis of this report because they had normal pulmonary vascular resistance immediately before operation. Two patients were included because at the time of their only preoperative catheterization study they had elevated resistance levels. Both patients had normal pulmonary vascular resistance at follow-up catheterization, even though one had markedly increased resistance in infancy.

Discussion

The aim of surgical treatment of ventricular septal defect, as of congenital heart disease in general, is the interruption of the natural history of the disease. This implies, therefore, that when pulmonary vascular disease is already present, surgery can be justified only when it can be demonstrated that the vascular changes regress, or at least no longer progress. What actually happens is still in dispute. Some workers[6–8] have shown a decrease in pulmonary vascular resistance—although not usually to normal levels—in every case, irrespective of the degree of preoperative elevation. One exceptional case has been reported[9] of a 4 year old boy with severe pulmonary hypertension and a bidirectional shunt through a ventricular septal defect who had normal pulmonary arterial pressure and resistance 8 months after successful surgery. Other workers[10,11] have found that although pulmonary arterial pressure decreased postoperatively, there was no significant change in resistance. Furthermore, as data based on longer postoperative fol-

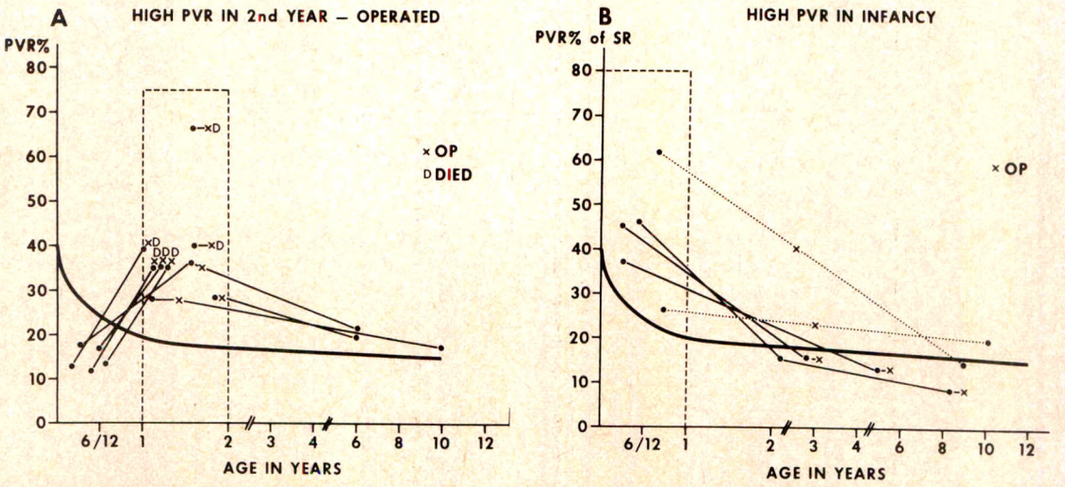

FIGURE 5. Natural and postoperative history of patients with increased pulmonary vascular resistance (PVR). **A,** patients with increased pulmonary vascular resistance in the second year of life, operated on before age 2 years. The heavy line represents the normal maturational line for pulmonary vascular resistance. There was a high mortality rate, but in the three survivors pulmonary vascular resistance returned to normal. **B,** patients with increased pulmonary vascular resistance in infancy, operated on later. All were found to have normal resistance later. In three **(solid lines),** a spontaneous decrease (before operation) was documented by preoperative catheterization study (see text).

low-up periods become available, it is clear that some patients have progressive pulmonary vascular disease in spite of closure of the ventricular septal defect.[4,14,15]

Factors influencing prognosis and mortality: In our series with follow-up periods as long as 11 years (mean 5 years), a change in resistance occurred in the majority of patients, in one direction or the other. Thus, a wide scatter in data has been found at follow-up catheterization. If one disregards the infant group and those operated on before age 2 years, the prognosis seems clearly related to the degree of preoperative elevation of pulmonary vascular resistance. The outcome is much more benign when the preoperative level is less than one third the systemic level. However, even in this group, an occasional patient will still experience progressive pulmonary vascular disease, a finding previously reported by DuShane et al.[4] A progressive increase in pulmonary vascular resistance and in clinical signs of pulmonary vascular disease seems to be the rule in patients whose preoperative pulmonary vascular resistance is more than one third the systemic level. Because of the clear-cut directional changes in pulmonary vascular resistance at follow-up study, the ultimate outcome seems clear in the majority of our cases. Only a few patients have shown little change in pulmonary vascular resistance. The two patients in this latter group who have been followed up for a very long time (6 and 11 years, respectively) are both doing very well clinically. Postoperative catheterization data indicate moderately increased pulmonary vascular resistance (35 and 42 percent, respectively), and these values are only slightly different from those obtained before operation (28 and 44 percent). One can speculate whether these patients truly had "arrested pulmonary vascular disease" and will lead normal lives with some degree of pulmonary hypertension.

That the presence of increased pulmonary vascular resistance results in a higher immediate postoperative mortality rate for closure of a ventricular septal defect has long been recognized. In our series it has been 32 percent; this is in striking contrast to the 7 percent mortality rate in our hospital for closure of a ventricular septal defect without associated increased resistance. Others[8,14,15] have reported a mortality rate for this procedure ranging from 15 to 50 percent depending on the degree of preoperative elevation of pulmonary vascular resistance. Castaneda et al.[6] found that the rate was reduced considerably when the defect was closed through the atrium, thus avoiding ventriculotomy (7 percent mortality in their series). Since the ventricular approach was used routinely in our series, we cannot comment on this issue.

Two thirds of the postoperative deaths occurred in the very young children (first to third years). Typically, these were children with a large ventricular septal defect and severe heart failure in infancy who underwent operation after manifesting pulmonary vascular disease very early in life. The combination of young age and increased pulmonary vascular resistance seemed to result in a very high operative mortality rate. We cannot comment on whether the rate would be lower for infants with increased pulmonary blood flow but normal resistance since in this hospital few such infants have undergone repair of the defect. Pulmonary artery banding has usually been preferred in this situation and has prevented the occurrence of early pulmonary vascular disease and permitted correction at a later time.

Increased pulmonary vascular resistance in the first and second year of life: Our data on patients operated on before age 2 years reveal several interesting facts. First, pulmonary vascular resistance returned to normal in the three survivors. Although this group is too small to permit definite con-

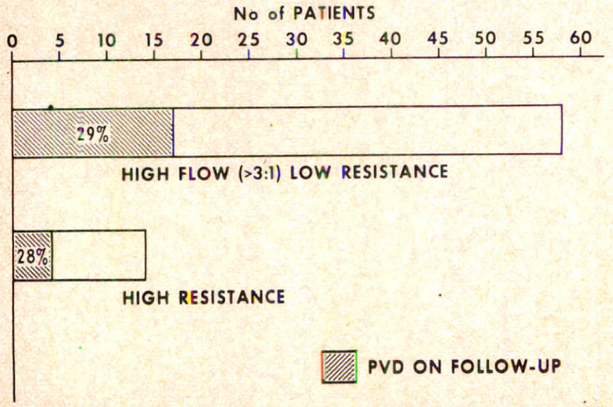

FIGURE 6. Prevalence of pulmonary vascular disease (PVD) in early childhood in patients who had increased pulmonary blood flow in infancy (more than three times systemic blood flow) and patients who had increased pulmonary vascular resistance in infancy (see text).

clusions, it is interesting that one of the three had a pulmonary vascular resistance of 38 percent before operation. Equivalent values in older children did not regress to normal postoperatively. This finding is in accord with recent data from the Mayo Clinic,[4] in which 13 patients with increased pulmonary vascular resistance operated on before age 2 years were later found to have normal pulmonary vascular resistance. Such data indicate that a large ventricular septal defect should be approached surgically very early in life, when pulmonary vascular disease is still reversible or has not yet developed. Primary closure is ideal if it can be performed with an acceptable mortality rate; the alternative is pulmonary artery banding to protect the pulmonary vascular bed and permit total correction later in life.

Increased pulmonary vascular resistance in early childhood was most often preceded in infancy by a phase of reduced resistance associated with a very high level of pulmonary blood flow. In these patients, the hemodynamic situation changed from one of increased pulmonary blood flow with reduced resistance in infancy to one of increased resistance and reduced blood flow in the second year of life. In contrast, of five patients with a high level of resistance in the first year of life, three had normal resistance on repeat preoperative catheterization; the two others were operated on without a repeat catheterization but had normal resistance values in the postoperative study. Whether closure of the ventricular septal defect was responsible for the decrease in resistance in these two cases is disputable. Indeed, all five cases could well represent instances of delayed pulmonary vascular maturation.

Two questions were raised by these patterns of evolution from infancy: (1) Does increased pulmonary vascular resistance in the first year of life invariably decrease spontaneously? (2) What percentage of infants with a ventricular septal defect, a very high flow ratio (pulmonary blood flow/systemic blood flow >3:1) and reduced pulmonary vascular resistance will have increased resistance in early childhood? These questions can be answered only by follow-up catheterization studies of patients who had these hemodynamic patterns in infancy but did not undergo surgery. In our patient material, we found 82 such cases (Fig. 6), of which 58 had a flow ratio of more than 3:1 and a resistance level below normal for age. In 29 percent of these, pulmonary vascular disease developed in early childhood. Since this prevalence is greater than that found in any other hemodynamic group,[16] these patients are clearly at high risk. Increased resistance in infancy (pulmonary vascular resistance above the normal maturational line) is uncommon at sea level: We found only 14 such cases. In 10 of these, resistance spontaneously returned to normal with an increase in pulmonary blood flow, but pulmonary vascular disease developed in 4, as determined by further increases in resistance values. Thus, although most of these patients will have a favorable course, this is another group that requires careful follow-up study.

Clinical Conclusions

The overall postoperative prognosis in ventricular septal defect with increased pulmonary vascular resistance, as found in our study, is obviously not good. In addition to the 18 operative deaths, there have been 7 late deaths, all almost certainly related to pulmonary vascular disease, as confirmed at autopsy in 5.

Fatalities occurred 1 to 7 years after operation and the patient's ages at death ranged from 7 to 16 years. This finding does not compare favorably with data on the natural history of nonsurgically treated Eisenmenger syndrome,[17,18] indicating that death is uncommon in the first and second decades, even with severe pulmonary vascular disease. Thus, in some patients, life expectancy is apparently shortened by the operation, even if they survive the procedure. On theoretical grounds, this finding is not unexpected; indeed, when pulmonary vascular resistance exceeds the systemic level, right to left shunting cannot occur after the defect is closed and the cardiac output becomes limited by the pulmonary vascular obstruction; suprasystemic pressures are then found in the pulmonary artery, as observed in two of our cases.

Finally, of the 32 long-term survivors (56 percent), 5 have evidence of progressive pulmonary vascular disease by both clinical and hemodynamic criteria, and 3 more have increased pulmonary vascular resistance not suspected clinically. Our data do not encourage operation in cases of moderately marked elevation of pulmonary vascular resistance, but rather call for interruption of the natural history before vascular obstructive changes of a significant degree are present. To be watched particularly closely are the high risk groups cited. Either pulmonary artery banding in the first year, or early surgical closure between the ages of 6 months and 2 years, should prevent irreversible pulmonary vascular damage from taking place. As results of open heart surgery in infants improve,[19,20] preference will probably be given to the latter procedure in many centers.

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Effect of Red Cell Volume Reduction on Pulmonary Blood Flow in Polycythemia of Cyanotic Congenital Heart Disease

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The acute effects of red cell volume reduction (erythropheresis) on pulmonary blood flow and pulmonary vascular resistance were measured in 16 patients with severe shunt-induced polycythemia. In subjects with D-transposition of the great arteries and no significant pulmonary stenosis (Group A) erythropheresis was associated with a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow and in mixing between the systemic and pulmonary circulations. Systemic arterial saturation decreased slightly. By contrast, erythropheresis in patients with severe pulmonary stenosis or atresia and a ventricular septal defect (Group B) was associated with a decrease in pulmonary blood flow and left to right shunt and an increase in right to left shunt. These alterations resulted in a significant reduction in systemic arterial oxygen saturation despite relatively little change in effective pulmonary blood flow. The acute hemodynamic effects of packed red cell transfusion in five patients with D-transposition of the great arteries, no significant pulmonary stenosis and relative anemia were more variable.

The observations in patients with shunt-induced polycythemia are probably related to a reduction in blood viscosity produced by a lowering of hematocrit concentration. The reduced viscosity decreases the impedance to flow in the systemic and pulmonary circulations. When pulmonary blood flow is largely derived from the systemic circuit, erythropheresis will diminish pulmonary flow and reduce systemic oxygen saturation. If the pulmonary blood flow is largely independent of the systemic circuit (as in D-transposition of the great arteries without pulmonary stenosis), an increase in total and effective pulmonary flow occurs.

Hypervolemia and an increase in red cell mass occurs in patients with congenital cardiac malformations as a compensatory response to the decreased arterial oxygen saturation.[1] The polycythemia is proportional to the severity of the hypoxemia which in turn is determined by the degree of right to left shunt, pulmonary blood flow and in some malformations (for example, D-transposition of the great arteries) by the systemic blood flow as well. Marked increases in hematocrit, which accompany severe polycythemia, lead to increased viscosity and shear stress and alterations in flow rate.[2] We have previously demonstrated that acute reduction in red cell volume with replacement of the blood withdrawn by plasma or albumin results in a decrease of blood viscosity, increased systemic blood flow, and an increase in the total amount of oxygen delivered to the tissues.[3] The purpose of this study was to determine the acute effect of red cell vol-

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ume reduction on pulmonary vascular resistance and flow in patients with severe shunt-induced polycythemia.

Methods

Twenty-one patients with cyanotic congenital heart disease, 16 with severe polycythemia and 5 with relative anemia, were studied in the catheterization laboratory. Demerol® compound (meperidine 25 mg, promethazine 6.25 mg, and chlorpromazine 6.25 mg/1 ml of mixture) in a dose of 1 ml/30 lb (maximal dose 2 ml) was administered before the study. The desired venous hematocrit value was achieved in the 16 polycythemic patients by replacement (erythropheresis) of whole blood with fresh plasma or 5 percent human albumin in physiologic saline solution and in the 5 anemic patients by transfusion with packed red blood cells. Details of the technique and method used in carrying out the reduction in red cell volume have been previously reported.[3] For transfusion, 8 to 11 ml/kg of packed red cells (hematocrit of blood 85 to 91 percent) was used.

Hemodynamic measurements were made with patients in the supine position after a 12 hour fast and before and approximately 1/2 to 1 hour after erythropheresis or packed cell transfusion. The hematocrit was determined on central venous blood and oxygen carrying capacity measured by the cyanmethemoglobin method. Blood oxygen saturation was determined by an oximeter (American Optical Corporation model 10840). Oxygen consumption was measured (Kipp method in 7 patients and Douglas bag collection in 14 patients) and systemic and pulmonary blood flow determinations were made in duplicate by the direct Fick principle. Mixed systemic venous (superior vena caval or right atrial) and arterial blood oxygen saturation and mixed pulmonary arterial and venous (pulmonary venous or left atrial in the absence of an atrial septal defect) blood were used for the calculation of systemic blood flow and pulmonary blood flow, respectively. In six patients blood oxygen contents were directly measured by the Lex-O_2-Con apparatus (Lexington Instrument Co., Waltham, Mass.). In the six patients with pulmonary atresia the saturation level of mixed pulmonary arterial blood was assumed to equal the systemic arterial oxygen saturation level, and in three patients the value for pulmonary venous blood saturation was assumed to be 96 percent. Arterial and venous pressures were obtained using strain gauge transducers, and the heart rate was monitored.

Effective pulmonary flow (EPF) and total right to left shunt were derived and calculated as follows:

$$\text{EPF} = \frac{\text{oxygen consumption (ml } O_2\text{/min per m}^2)}{\text{pulmonary venous oxygen content (ml } O_2\text{/liter) minus mixed systemic oxygen content (ml } O_2\text{/liter)}} \quad (1)$$

$$\text{Total left to right shunt} = \text{pulmonary blood flow (liters/min per m}^2\text{) minus effective pulmonary flow (liters/min per m}^2\text{)} \quad (2)$$

$$\text{Total right to left shunt} = \text{systemic blood flow minus effective pulmonary flow} \quad (3)$$

The effective pulmonary flow may be defined as the flow necessary to carry metabolic oxygen requirements if systemic mixed venous blood alone were perfusing the lung.[4] In patients with D-transposition of the great arteries and absence of severe pulmonary stenosis, effective pulmonary flow = left to right shunt = right to left shunt. The data on 8 of the 21 patients have been previously published in part.[3]

The results were analyzed using standard statistical equations. All tests for significance were based on paired *t* statistics.

Results

Effects of Red Cell Volume Reduction

The acute effects of red cell volume reduction on pulmonary blood flow and systemic blood flow in patients with severe polycythemia due to cyanotic congenital heart disease are summarized in Table I. The 16 patients with polycythemia were classified into two groups on the basis of their response patterns. Group A comprised 5 patients with D-transposition of the great arteries with intact ventricular septum (or small septal defect) and no significant pulmonary stenosis, and Group B comprised 11 patients with se-

TABLE I

Effects of Acute Red Cell Volume Reduction on Blood Flow in 16 Patients With Severe Polycythemia Due to Shunt Hypoxemia

Variable	Group A (5 patients) Mean ± Standard Deviation			Group B (11 patients) Mean ± Standard Deviation		
	Before	After	*P* Value	Before	After	*P* Value
Hematocrit (%)	76 ± 6	66 ± 6	...	74 ± 4	63 ± 5	...
Oxygen capacity (vol. %)	28.7 ± 2.9	23.2 ± 3.0	0.02–0.05	30.6 ± 1.9	26.1 ± 1.9	0.01
Systemic oxygen saturation (%)	70.2 ± 3.6	67.7 ± 5.0	0.1	78.2 ± 7.4	72.1 ± 8.0	0.01
Oxygen consumption (ml/min per m²)	169 ± 35	172 ± 27	0.50	147 ± 27	141 ± 25	0.10–0.50
Heart rate (beats/min)	107 ± 21	109 ± 13	0.50	101 ± 11	100 ± 11	0.50
Systemic blood flow (liters/min per m²)	4.2 ± 1.8	7.1 ± 3.0	0.10–0.05	3.1 ± 1.1	4.7 ± 1.9	0.01
Pulmonary blood flow (liters/min per m²)	8.5 ± 0.6	12.5 ± 3.3	0.05–0.02	3.7 ± 1.7	3.0 ± 1.3	0.01
Effective pulmonary flow (liters/min per m²)	1.4 ± 0.3	1.9 ± 0.5	0.01	1.5 ± 0.4	1.5 ± 0.4	0.50
Right to left shunt (liters/min per m²)	1.4 ± 0.3	1.9 ± 0.5	0.01	1.6 ± 0.9	2.7 ± 1.6	0.01
Systemic vascular resistance (mm Hg/liter per min per m²)	19.6 ± 6.7	11.7 ± 5.8	0.02	29.4 ± 12.5	19.3 ± 8.5	0.01
Pulmonary vascular resistance (mm Hg/liter per min per m²)	4.0 ± 3.3	2.7 ± 2.3	0.10–0.05	...	...	...

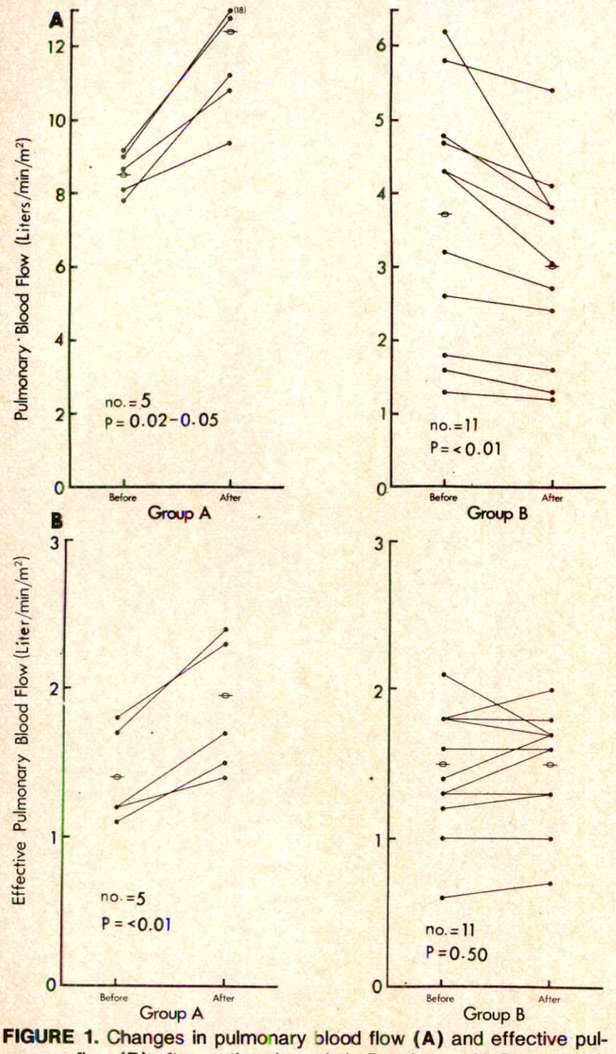

FIGURE 1. Changes in pulmonary blood flow **(A)** and effective pulmonary flow **(B)** after erythropheresis in 5 patients with D-transposition of the great arteries (D-TGA) and no pulmonary stenosis (Group A), and 11 patients with severe pulmonary stenosis or atresia and normally or abnormally related great arteries (Group B). The **hatched oval** symbols denote mean values before and after the procedure.

vere pulmonary stenosis or pulmonary atresia, ventricular septal defect and normally or abnormally related great arteries.

The presence of a steady state during the study was suggested by the lack of significant changes in heart rate, oxygen consumption, respiratory rate, temperature or level of activity. The mean initial venous hematocrit in patients in Group A was reduced from 76 percent (range 66 to 84) to 66 percent (range 61 to 76) and in Group B from 74 percent (range 65 to 80) to 63 percent (range 53 to 69). The mean oxygen carrying capacity in patients in Group A was reduced from 28.7 vol. percent (range 25.5 to 32.1) to 23.2 vol. percent (range 20.9 to 25.0) and in Group B from 30.6 vol. percent (range 28.5 to 33.7) to 26.1 vol. percent (range 21.9 to 28.4). Reduction of the red cell volume by replacement with fresh frozen plasma or 5 percent albumin has been previously demonstrated to result in only a minimal decrease in total blood volume.[3]

Group A (D-transposition of the great arteries without significant pulmonary stenosis): Three of the five patients had pulmonary arterial hypertension and two had normal pulmonary arterial pressure. The reduction in hematocrit was associated with a decrease in systemic vascular resistance in all patients (P <0.02) from an initial mean of 19.6 ± 6.7 to 11.7 ± 5.8 mm Hg/liter per min per m^2. The mean systemic blood flow increased in all patients (P = 0.10 to 0.05) from 4.2 ± 1.8 to 7.1 ± 3.0 liters/min per m^2. Changes in the pulmonary circulation paralleled those in the systemic circuit. Pulmonary blood flow increased in all patients (P = 0.05 to 0.02) from a mean of 8.5 ± 0.6 to 12.5 ± 3.3 liters/min per m^2 (Fig. 1A) and pulmonary vascular resistance decreased in all patients (P = 0.05 to 0.10) from a mean of 4.0 ± 3.3 to 2.7 ± 2.3 mm Hg/liter per min per m^2. The reduction in red cell volume was also accompanied by an increase in shunting between the pulmonary and systemic circulations (P <0.01). The right to left shunt (equal to left to right shunt or effective pulmonary flow) increased from a mean of 1.4 ± 0.3 to 1.9 ± 0.5 liters/min per m^2 (Fig. 1B). However, systemic arterial saturation decreased slightly (P = 0.1) from an initial mean of 70.2 ± 3.6 to 67.7 ± 5.0 percent.

Group B (pulmonary stenosis or pulmonary atresia and a ventricular septal defect with normally or abnormally related great arteries): All 11 patients in Group B had very severe pulmonary stenosis or atresia with a large right to left shunt through a ventricular septal defect. Reduction in hematocrit resulted in a decrease in systemic vascular resistance in all patients (P <0.01), from a mean of 29.4 ± 12.5 to 19.3 ± 8.5 mm Hg/liter per min per m^2 and an increase in systemic blood flow (P <0.01) from a mean of 3.1 ± 1.1 to 4.7 ± 1.9 liters/min per m^2. However, in contrast to results in patients in Group A, pulmonary blood flow decreased in all patients (P <0.01) from a mean of 3.7 ± 1.7 to 3.0 ± 1.3 liters/min per m^2 (Fig. 1A). The decrease in pulmonary blood flow was associated with a decrease in left to right shunted blood from a mean of 2.2 ± 1.5 to 1.5 ± 1.1 liters/min per m^2 (P <0.01). Since most of the patients had pulmonary atresia, pulmonary arterial pressure could not be measured and resistance was therefore not calculated. The increase in systemic blood flow was accomplished by an increase in intracardiac right to left shunting in all patients (P <0.01) from a mean of 1.6 ± 0.9 to 2.7 ± 1.6 liters/min per m^2. In two patients with D-transposition of the great arteries, ventricular septal defect and severe pulmonary stenosis, the right to left shunt was assumed to equal systemic flow minus effective pulmonary flow. The overall results for Group B, however, would not be significantly altered if right to left shunt were assumed to equal effective pulmonary flow. Calculation of pulmonary blood flow in these patients may be somewhat inaccurate because of the probability of increased collateral pulmonary circulation and the difficulty in obtaining an accurate mixed pulmonary arterial blood sample.

The decrease in pulmonary flow and increase in right to left shunt resulted in a reduction in arterial oxygen saturation from 78.1 ± 7.4 to 72.1 ± 8.0 percent (P <0.01). The effective pulmonary blood flow remained essentially unchanged (P = 0.50) (Fig. 1B), possibly because of insignificant changes in mean mixed venous saturation from 61.6 ± 7.7 to 59.6 ± 6.7 percent. Erythropheresis did not alter the pulmonary venous blood oxygen saturation in either group.

The procedure was not associated with any serious complications and was well tolerated by the patients.

Effects of Transfusion with Packed Red Cells

The acute effects of red cell transfusion on systemic and pulmonary flow in five patients with D-transposition of the great arteries are summarized in Table II. The mean hematocrit was increased from 44.6 ± 6.1 to 49.2 ± 5.9 percent (P <0.01) and mean oxygen carrying capacity from 17.1 ± 3.5 to 19.2 ± 3.0 vol. percent (P <0.01). The increase in the venous hematocrit and carrying capacity was accompanied by an increase in systemic vascular resistance and reduction in systemic flow in all patients. Mean systemic vascular resistance increased from 11.1 ± 1.6 to 15.3 ± 3.2 mm Hg/liter per min per m^2 (P = 0.01 to 0.02) and systemic flow decreased from 5.8 ± 1.2 to 4.6 ± 0.7 liters/min per m^2 (P = 0.01 to 0.02). The acute effects on pulmonary flow and vascular resistance were not marked and were more variable. Pulmonary blood flow increased slightly (P = 0.4) and pulmonary resistance decreased slightly (P = 0.5) in four of five patients. The acute transfusion resulted in less mixing between the systemic and pulmonary circulations. Mean effective pulmonary flow decreased from 2.9 ± 1.1 to 2.4 ± 0.6 liters/min per m^2 (P = 0.05 to 0.1). Systemic arterial oxygen saturation was essentially unchanged by the procedure, but when measured (by an air oximeter) 24 to 48 hours later had increased by 2 to 7 percent (mean 5).

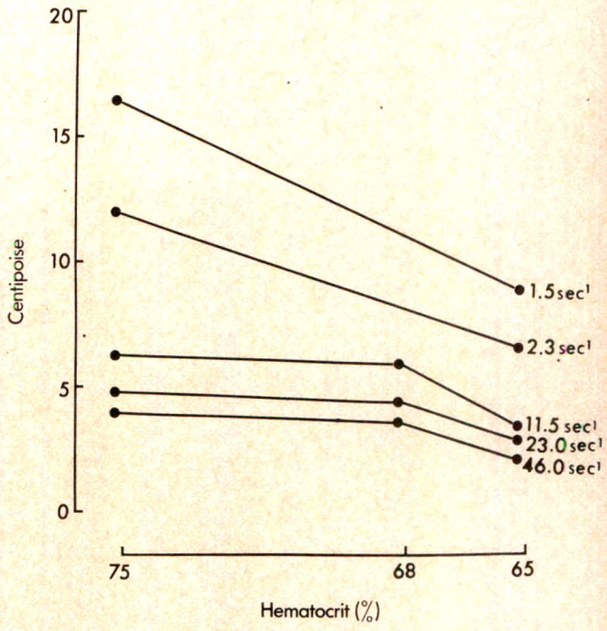

FIGURE 2. Changes in blood viscosity at various shear rates associated with erythropheresis in a patient with polycythemia and D-transposition of the great arteries.

Discussion

Red cell pheresis: Polycythemia in some patients with cyanotic congenital heart disease may become so severe that the advantages of increased oxygen carrying capacity are offset by adverse physiologic effects, the development of hyperviscosity, with consequent thromboses or infarctions in vital organs, and frequently a bleeding diathesis.[5–8] In a previous study[3] we have shown that red cell volume reduction in these patients results in decreased blood viscosity, reduced systemic vascular resistance, increased systemic flow and improved systemic oxygen transport. The present study indicates that acute red cell volume reduction in polycythemic patients with D-transposition of the great arteries without a large ventricular septal defect or significant pulmonary stenosis results in a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow. The de-

TABLE II

The Effects of Red Cell Transfusion on Blood in Five Patients With D-Transposition of the Great Arteries

	Mean ± Standard Deviation		
	Before	After	*P* Value
Hematocrit (%)	45 ± 6	49 ± 6	...
Oxygen capacity (vol. %)	17.1 ± 3.5	19.2 ± 3.0	0.01
Systemic oxygen saturation (%)	75.8 ± 4.9	76.0 ± 4.4	0.3–0.4
Oxygen consumption (ml/min per m^2)	175 ± 37	178 ± 24	0.7
Heart rate (beats/min)	126 ± 21	126 ± 20	0.8
Systemic blood flow (liters/min per m^2)	5.8 ± 1.2	4.6 ± 0.7	0.01–0.02
Pulmonary blood flow (liters/min per m^2)	15.3 ± 7.3	13.9 ± 4.1	0.5
Effective pulmonary flow (liters/min per m^2)	2.9 ± 1.1	2.4 ± 0.6	0.05–0.10
Right to left shunt (liters/min per m^2)	2.9 ± 1.1	2.4 ± 0.6	0.05–0.10
Systemic vascular resistance (mm Hg/liters per min per m^2)	11.1 ± 1.6	15.2 ± 3.1	0.01–0.02
Pulmonary vascular resistance (mm Hg/liters per min per m^2)	1.9 ± 1.7	2.0 ± 2.2	0.5

creased resistance is probably secondary to the reduced blood viscosity that accompanies the reduction in hematocrit. The decrease in viscosity is greatest at low shear rates, that is, those present at the level of the small arterioles and venules,[2] where it might be expected to have the greatest influence on reducing the resistance to flow. The effect of erythropheresis on reducing viscosity at various shear rates is illustrated in Figure 2.

There was also a significant increase in effective pulmonary flow or mixing between the systemic and pulmonary circulations. Despite the improved mixing, systemic arterial oxygen saturation decreased slightly because of the increase in systemic blood flow and reduction in oxygen carrying capacity. The systemic arterial saturation in patients with D-transposition of the great arteries depends not only on the degree of mixing between the pulmonary and systemic circulations, but also on the systemic blood flow and hemoglobin concentration.[4] The effect of an increase in the rate of recirculated systemic flow (systemic venous return) and reduction of hemoglobin concentration thus results in a slightly lower level of systemic arterial saturation despite the improved mixing.

In contrast to polycythemic patients with transposition of the great arteries without pulmonary stenosis (Group A), patients with pulmonary atresia or severe pulmonary stenosis and ventricular septal defect (Group B) manifested a reduction in pulmonary blood flow after red cell pheresis. Because pulmonary blood flow in these patients is supplied totally or predominantly from the systemic circulation, a reduction in the systemic vascular resistance results in a decrease of the left to right shunt through a surgically created anastomosis or the extensive aortopulmonary collateral circulation. The decrease in systemic vascular resistance must be relatively greater than that of the already reduced resistance of the pulmonary circuit. The increase in systemic blood flow is accomplished by an increased right to left shunt through the ventricular septal defect. Despite the reduced pulmonary blood flow, effective pulmonary blood flow is essentially unchanged, but because of the greater right to left shunt there is a significant decrease in the systemic arterial oxygen saturation. The ability to increase the total amount of oxygen delivered to the tissues per unit of time, or systemic oxygen transport, will then be totally dependent on the ability to increase cardiac output.[3] Excessive reduction in the hematocrit in these patients may lead to severe hypoxemia, and erythropheresis should therefore be performed with great care.

Red cell transfusion: In patients with D-transposition of the great arteries, a relatively small increase in hematocrit and oxygen carrying capacity after red cell transfusion resulted in a significant increase in systemic vascular resistance and decrease in systemic flow (Table II). The effect of the transfusion on pulmonary flow, effective pulmonary flow and systemic arterial oxygen saturation was more variable. Effective pulmonary flow showed a tendency to decrease and systemic arterial saturation remained essentially unchanged by the procedure. However, our data are from a small group of patients and do not exclude the possibility of an effect on pulmonary flow and systemic saturation. Clinical follow-up studies of patients with D-transposition of the great arteries who have been given transfusion suggest that the procedure does increase systemic saturation and reduce congestive heart failure. An increase in systemic oxygen saturation was seen in our patients within 24 hours after the transfusion.

Clinical implications: The hemodynamic effects reported here are acute in nature, and after a period of adjustment and fluid equilibrium between the vascular and extravascular compartments a different hemodynamic state may exist. Erythropheresis in our experience is helpful in reducing complications during the operative and postoperative periods[9] and in treating some of the more serious complications of severe polycythemia.[10] Since the calculated ratio of systemic to pulmonary vascular resistance can be significantly altered by changes in the hematocrit and hemoglobin, criteria for operability based on these variables should take into consideration the hemodynamic state at the time the resistance levels were measured. The transfusion of packed red cells in a patient with D-transposition of the great arteries and relative anemia may not immediately improve the arterial saturation, but a benefit may be apparent a few days later. We believe the procedure is indicated in all patients who have lost a considerable amount of blood (at catheterization, for example) or are relatively anemic.

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Bypass Graft Surgery Versus Medical Therapy of Angina Pectoris

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Forty patients with angina pectoris (New York Heart Association functional class III) despite medical therapy were studied. Twenty who underwent coronary bypass graft surgery and 20 comparable patients treated only medically underwent exercise tests during the control period and 3, 6, 9 and 12 months later. One of 20 surgically treated patients (5 percent) died at operation. One year mortality rates were 10 percent (2 of 20 surgically treated patients) and 5 percent (1 of 20 medically treated patients). Three of 20 patients (15 percent) had a myocardial infarction at operation. By 1 year, 4 of 20 surgically treated patients (20 percent) and 1 of 20 medically treated patients (5 percent) had had a myocardial infarction. At 1 year, 18 of 27 grafts (67 percent) were patent. Three and 6 months after the control period, no angina after exercise, a more than 25 percent increase in exercise performance until angina, and an increase in the value for product of systolic blood pressure times heart rate occurred in significantly more surgically than medically treated patients. One year after the control period, 14 of 18 surgically treated patients (78 percent) and 10 of 19 medically treated patients (53 percent) had no angina after exercise or a more than 25 percent increase in exercise performance until angina. One year after the control period, 4 of 16 medical patients (25 percent) and 6 of 15 surgical patients (40 percent) not receiving digitalis had no postexercise ischemic S–T segment depression. These data suggest that the coronary artery bypass operation should be considered only if medical therapy fails to relieve disabling angina.

The advent of aortocoronary saphenous vein bypass graft surgery has been welcomed by the medical profession. However, the indications for this procedure are not firmly agreed upon. Until results of controlled clinical trials[1,2] provide the data needed to formulate these indications properly, recommendations for this operation must be made with caution.[3]

We performed saphenous vein coronary artery bypass graft surgery in 20 of 40 patients who had angina pectoris (functional class III, New York Heart Association) despite medical management. The other 20 patients continued to receive medical therapy. The medical and surgical groups were comparable in angiographic evidence of significant coronary artery disease, myocardial function and risk factors for coronary artery disease. Physiologic studies were performed in both groups during the control period and 3, 6, 9 and 12 months later. Coronary angiography, left ventricular cineangiography and left heart catheterization were also performed in all surviving surgically treated patients 1 year postoperatively. This paper presents the data from this study.

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Subjects and Methods

Case Material

The surgical group consisted of 19 men and 1 woman with a mean age of 50 ± 4 years (standard deviation). The medical group consisted of 20 men with a mean age of 50 ± 5 years. The surgically treated patients and the patients chosen for continued medical management were matched case by case to provide comparability. All 40 patients had functional class III angina pectoris despite medical management (including administration of nitroglycerin, sublingually and at least 120 mg daily of propranolol, orally). All had at least one bypassable significant coronary arterial lesion with good patent distal runoff. Significant single vessel disease (greater than 50 percent luminal narrowing) was present in 4 of the 20 patients (20 percent) in each group. Significant multivessel disease was present in the other 32 patients. The mean ejection fraction was 52 percent in both the medical and surgical groups.

Eleven of the 20 surgically treated patients (55 percent) and 12 of the 20 medically treated patients (60 percent) had documented old healed myocardial infarction. Mild hypertension (blood pressure between 140/90 and 160/100 mm Hg) was present in 2 surgically treated patients (10 percent) and in 3 medically treated patients (15 percent). One patient (5 percent) in each group was a cigarette smoker on entering the study. Twelve surgically treated patients (60 percent) and 14 medically treated patients (70 percent) had a serum cholesterol level above 250 mg/100 ml. Twelve surgically treated patients (60 percent) and 10 medically treated patients (50 percent) had an elevated serum triglyceride level (above 150 mg/100 ml). A type IV lipoprotein pattern was present in 8 surgically treated patients (40 percent) and 7 medically treated patients (35 percent). A type II lipoprotein pattern was present in 3 patients (15 percent) in each group. Only 1 of the 40 patients (in the medical group) was receiving medication (phenformin) for diabetes mellitus.

All 40 patients selected for this study demonstrated ischemic S–T segment depression greater than or equal to 1 mm below the resting level after exercise-induced angina. Three patients in each group received digitalis during the control and study periods.

Protocol

Exercise testing: Before the study, the patients were taken to the laboratory where they were familiarized with the equipment and the procedure and practiced upright exercise on a constant-load Collins bicycle ergometer with a progressive work load.[4]

During the control period and 3, 6, 9 and 12 months after operation or continued medical management, all surviving patients performed the following exercise protocol at 8 AM in the fasting state. Leads V_5, aVF and I were recorded in that order with an electrocardiograph with the subject in the supine position. An electrocardiogram with a modified lead V_5 was then recorded with the patient sitting upright on the Collins bicycle ergometer, and the resting heart rate was obtained from this electrocardiogram. The resting blood pressure was then measured with a mercury sphygmomanometer with the patient sitting upright on the bicycle ergometer.

Each patient then exercised upright on the constant-load bicycle ergometer with a progressive work load[4] until the onset of angina, and the duration of exercise was recorded with a stopwatch. If angina did not develop, the patient exercised until the onset of marked fatigue. Blood pressure and heart rate at the onset of angina or marked fatigue were recorded with the patient sitting upright on the bicycle ergometer. An electrocardiogram with a modified lead V_5 was recorded immediately after angina or marked fatigue with the patient in the upright position. Leads V_5, aVF and I in that order were then recorded while the patient was in the supine position immediately after angina or marked fatigue and 1, 2, 3, 4, 5 and 6 minutes later.

No patient smoked or took antianginal medication on the morning of the exercise tests. The electrocardiograms were coded and analyzed after the study was completed by an investigator who did not know from whom or when the tracings were obtained.

Coronary arteriography and ventriculography: One year after operation, coronary arteriography was performed by either the Judkins[5] or the Sones[6] method in all surviving surgical patients. Three views of each coronary vessel (including the right and left anterior oblique views) were obtained. Selective opacification of the bypass graft was performed in at least 2 views (right and left anterior oblique) in all surviving surgical patients. These films were reviewed at weekly cardiac catheterization conferences by cardiology staff members, cardiac surgeons and a cardiac radiologist. The interpretation of these films was based on group consensus.

One year after operation, all surviving surgical patients also underwent left heart catheterization and left ventricular cineangiography. Left ventriculography was performed in the 45° right anterior oblique projection. Left ventricular end-diastolic and end-systolic volumes were computed from angiographic films exposed in the right anterior oblique projection. Frames showing premature ventricular beats or short runs of tachycardia or frames within two beats after the premature ventricular beats were excluded. In all patients, both the left ventricular margin and a clearly defined left ventricular apex and aortic valve plane were clearly delineated.

The ejection fraction was calculated from the formula:

$$EF = (EDV - ESV)/EDV$$

where EF = ejection fraction, EDV = end-diastolic volume and ESV = end-systolic volume.[7] The ejection fractions were calculated by fellows in cardiology.

Results

Mortality: One of the 20 surgically treated patients (5 percent) died at operation. One patient each (5 percent) in the medical and surgical groups died of myocardial infarction during the 1 year follow-up period. The 1 year surgical mortality rate of 10 percent (2 of 20 patients) was not significantly different from the 1 year medical mortality rate of 5 percent (1 of 20 patients((chi-square = 0.36; $P > 0.05$).

Myocardial infarction: Three of 20 surgically treated patients (15 percent) had a transmural myocardial infarction at the time of operation, with new pathologic Q waves that persisted. In these three patients an area of asynergy due to postoperative myocardial infarction was noted on the left ventriculogram obtained 1 year postoperatively. These myocardial infarctions occurred in the region supplied by the bypassed artery. The 20 percent rate of myocardial infarction at 1 year in the surgical group (4 of 20 patients) was not significantly different from the 5 percent rate of myocardial infarction at 1 year in the medical group (1 of 20 patients) (chi-square = 2.06; $P > 0.05$).

Exercise performance until angina: Table I shows the data on exercise performance until angina for the 19 survivors in the surgical group and the 20 medically treated patients during the control period and during repeat testing performed 3, 6, 9 and 12 months later.

At 3 months, 11 of 19 surgically treated patients (58 percent) were angina-free after exercise compared with none of 20 medically treated patients (chi-square = 16.13; $P < 0.001$). At 3 months, 16 of 19 surgically treated patients (84 percent) had no angina after exercise or a more than 25 percent increase in exercise performance until angina compared with 5 of 20 medically treated patients (25 percent) (chi-square = 13.75; $P < 0.001$).

At 6 months, 8 of 19 surgically treated patients (42 percent) had no angina after exercise compared with 1 of 19 medically treated patients (5 percent) (chi-square = 7.13; $P < 0.01$). At 6 months, 15 of 19 surgically treated patients (79 percent) had no angina

TABLE I

Duration of Exercise Performance Until Angina in 19 Survivors of Surgery and 20 Medically Treated Patients

Case no.	Control Duration (sec)	3 Months		6 Months		9 Months		1 Year	
		Duration (sec)	% Change from Control	Duration (sec)	% Change from Control	Duration (sec)	% Change from Control	Duration (sec)	% Change from Control
A. Surgically Treated Patients									
1	186	573	+208	498	+168	412	+122	457	+146
2	189	259	+37	277	+47	318	+68	369	+95
3	182	131	−28	166	−9	241	+32	273	+50
4	180	No A		208	+16	Dead			
5	190	219	+15	225	+18	174	−8	130	−32
6	176	No A		No A		No A		No A	
7	201	No A		No A		No A		No A	
8	214	No A		No A		No A		No A	
9	188	199	+6	179	−5	212	+13	197	+5
10	181	No A		331	+83	264	+46	394	+118
11	260	No A		No A		No A		No A	
12	195	No A		412	+111	239	+23	174	−11
13	219	No A		No A		No A		No A	
14	189	No A		No A		No A		No A	
15	224	347	+55	363	+62	390	+74	487	+117
16	193	301	+56	264	+37	211	+9	199	+3
17	185	298	+61	271	+46	248	+34	267	+44
18	217	No A		No A		No A		No A	
19	183	No A		No A		No A		No A	
B. Medically Treated Patients									
1	192	231	+20	217	+13	204	+6	221	+15
2	181	237	+31	289	+60	378	+109	340	+88
3	203	189	−7	176	−13	Crescendo angina		141	−31
4	199	228	+15	216	+9	223	+12	311	+56
5	182	176	−3	194	+7	170	−7	218	+20
6	204	283	+39	517	+153	No A		No A	
7	178	209	+17	215	+21	217	+22	209	+17
8	196	380	+94	238	+21	312	+59	233	+19
9	183	221	+21	335	+83	351	+92	286	+56
10	192	181	−6	177	−8	225	+17	269	+40
11	219	364	+66	No A		No A		No A	
12	230	263	+14	248	+8	217	−6	194	−16
13	180	211	+17	356	+98	506	+181	483	+168
14	187	180	−4	198	+6	294	+57	329	+76
15	199	142	−29	138	−31	130	−35	125	−37
16	214	353	+65	411	+92	698	+226	No A	
17	206	225	+9	Dead					
18	185	219	+18	214	+16	236	+28	323	+75
19	188	218	+16	361	+92	349	+86	391	+108
20	210	254	+21	232	+10	219	+4	248	+18

No A = no angina.

TABLE II

Mean Product of Systolic Blood Pressure Times Heart Rate ± 1 Standard Deviation/100 After Exercise in the Surgical and Medical Groups

		3 Months		6 Months		9 Months		1 Year	
	Control Value	Value	% Change* from Control	Value	% Change from Control	Value	% Change from Control	Value	% Change from Control
Surgical	194.3 ±20.7	242.4 ±40.4	+25	243.1 ±38.4	+25	239.4 ±38.0	+23	235.3 ±39.3	+21
Medical	197.3 ±15.1	205.5 ±17.7	+4	209.6 ±27.0	+6	217.6 ±31.7	+10	218.3 ±33.5	+11

after exercise or a more than 25 percent increase in exercise performance until angina compared with 7 of 19 medically treated patients (37 percent) (chi-square = 6.91; $P < 0.01$).

At 9 months, 8 of 18 surgically treated patients (44 percent) had no angina after exercise compared with 2 of 19 medically treated patients (11 percent) (chi-square = 5.39; $P < 0.05$). At 9 months, 14 of 18 surgically treated patients (78 percent) had no angina after exercise or a more than 25 percent increase in exercise performance until angina compared with 10 of 19 medically treated patients (53 percent) (chi-square = 2.56; $P > 0.05$).

At 1 year, 8 of 18 surgically treated patients (44 percent) had no angina after exercise compared with 3 of 19 medically treated patients (16 percent) (chi-square = 3.63; $P > 0.05$). At 1 year, 14 of 18 surgically treated patients (78 percent) had no angina after exercise or a more than 25 percent increase in exercise performance until angina compared with 10 of 19 medically treated patients (53 percent) (chi-square = 2.56; $P > 0.05$).

Excluding digitalized patients, at 1 year, 4 of 16 medical patients (25 percent) and 6 of 15 surgical patients (40 percent) had less than 1 mm of ischemic S–T segment depression after exercise (chi-square = 0.80; $P > 0.05$).

Systolic blood pressure-heart rate product: Table II shows the mean product of systolic blood pressure times heart rate ± 1 standard deviation/100 after exercise for the 18 one-year survivors in the surgical group and the 19 one-year survivors in the medical group during the control period and 3, 6, 9 and 12 months later. This table also shows the percent increase in mean product of systolic blood pressure times heart rate after exercise for the 1 year survivors in the surgical and medical groups 3, 6, 9 and 12 months from the control period.

In the surgical group, the product of systolic blood pressure times heart rate after exercise showed a mean increase of 25 percent at 3 months ($t = 4.75$; $P < 0.001$), 25 percent at 6 months ($t = 5.05$; $P < 0.001$), 23 percent at 9 months ($t = 4.66$; $P < 0.001$) and 21 percent at 12 months ($t = 4.25$; $P < 0.001$).

In the medical group, a significant increase in mean product of systolic blood pressure times heart rate after exercise occurred after the control period; this increase was 4 percent at 3 months ($t = 2.43$; $P < 0.05$), 6 percent at 6 months ($t = 2.44$; $P < 0.05$), 10 percent at 9 months ($t = 3.17$; $P < 0.01$) and 11 percent at 12 months ($t = 3.10$; $P < 0.01$). The mean product of systolic blood pressure times heart rate after exercise was significantly greater in the surgical group than in the medical group at 3 months ($t = 3.67$; $P < 0.001$) and at 6 months ($t = 3.11$; $P < 0.01$) but not at 9 or 12 months.

The mean ejection fraction for the 18 surviving surgical patients at 1 year was 54.8 ± 6.7 percent compared with 52.2 ± 6.3 percent before operation ($t = 2.06$; $P > 0.05$).

Eighteen of the 27 grafts (67 percent) were patent at 1 year. Sixteen of 18 patients (89 percent) who survived 1 year after operation had at least one patent graft. Surgical Patient 5 (Table I) had two of two grafts occluded, and the 1 year follow-up coronary arteriograms demonstrated occlusion of the single graft of Patient 9. Patient 3 had two of two grafts patent 3 months postoperatively, and one of these grafts was patent 1 year after operation. Patient 4, who died 8.5 months after operation, had patency of his single graft 6 months after operation.

Discussion

Postoperative Myocardial Infarction

Myocardial infarction documented by the appearance of significantly abnormal Q waves on the electrocardiogram or by autopsy has been reported to occur at the time of coronary artery bypass graft surgery by several investigators. The finding was noted in 3 of their last 30 patients (10 percent) by Hultgren et al.,[8] in 23 of 100 patients (23 percent) by Williams et al.,[9] in 15 of 151 patients (10 percent) by Kansal et al.,[10] in 11 of 37 patients (30 percent) by Espinoza et al.,[11] in 7 of 102 patients (7 percent) by Alderman et al.,[12] in 53 of 480 patients (11 percent) by Morris et al.,[13] in 11 of 38 patients (29 percent) by Guiney et al.,[14] in 8 of 46 patients (17 percent) by Anderson et al.[15] and in 3 of our 20 patients (15 percent). Anderson et al.[15] reported that the postoperative vectorcardiogram showed new myocardial infarction in 6 of 17 patients (35 percent). Hultgren et al.[8] also found elevation of serum glutamic oxaloacetic transaminase levels above 90 units in 12 of their last 30 patients (40

percent) and lactic dehydrogenase levels exceeding 900 units in 10 of these 30 patients (33 percent) after saphenous vein coronary bypass graft surgery. They considered serum enzyme elevations of this degree to be diagnostic of acute myocardial infarction.

Brewer et al.[16] reported that 27 of 252 patients (11 percent) undergoing saphenous vein coronary artery bypass graft surgery died. Ten of the 17 patients (57 percent) who underwent autopsy after operation were found to have acute myocardial infarction. One patient who died but did not undergo autopsy had electrocardiographic evidence of acute myocardial infarction. Forty-nine of their 243 patients (20 percent) had a new myocardial infarction documented by autopsy or by postoperative electrocardiography.

In light of the high rate of postoperative myocardial infarction in these reported series,[8–16] the evidence does not justify performance of coronary artery bypass graft surgery to prevent myocardial infarction in patients with stable angina.

Objective Improvement with Surgical or Medical Therapy

Our data show absence of angina after exercise in significantly more surgically than medically treated patients at 3, 6, and 9 months but not at 12 months after the control period. Our data also show absence of angina or a greater than 25 percent increase in exercise performance until angina in significantly more surgically than medically treated patients at 3 and 6 months but not at 9 or 12 months after the control period. One year after the control period, absence of angina after exercise or a greater than 25 percent increase in exercise performance until angina occurred in 14 of 18 surgically treated patients (78 percent) and in 10 of 19 patients (53 percent) who continued to receive the same medical management. The trend toward alleviation of angina by medical therapy alone shown by these data indicates the importance of conducting controlled clinical trials in evaluating therapeutic regimens.

An increase in the product of systolic blood pressure times heart rate, presumptively indicating increased oxygen delivery to the ischemic myocardium, was also significantly higher in our surgical group than in our medical group at 3 and 6 months but not at 9 or 12 months after the control period. One year after the control period, an increase of 21 percent in mean product of systolic blood pressure times heart rate occurred in the surgical group compared to an 11 percent increase in the medical group.

Six of the 15 surgically treated patients (40 percent) and 4 of the 16 medically treated patients (25 percent) not receiving digitalis had ischemic S–T segment depression greater than or equal to 1 mm during the control period but no evidence of ischemic S–T segment depression 1 year later. These data also indicate the need to conduct controlled clinical trials in evaluating therapeutic regimens.

Amsterdam et al.[17] found that 6 to 10 weeks after coronary artery saphenous vein bypass graft surgery, angina could not be provoked by exercise in 20 of 20 patients with severe angina pectoris. The mean product of the systemic intraarterial pressure times heart rate increased from 144 to 179 (24 percent) in these 20 patients. These investigators also stated that electrocardiographic ischemic ST–T changes of exercise cleared or decreased.

Bartel et al.[18] found in 92 patients tested with maximal graded treadmill exercise tests 2 to 20 months after aortocoronary bypass surgery that 64 percent exercised longer and that 49 percent achieved higher maximal heart rates. Twenty-eight of their 62 patients (45 percent) who preoperatively had ischemic S–T segment depression of 1 mm after exercise had normal exercise electrocardiograms in the postoperative follow-up study.

Miller et al.[19] restudied 12 to 28 months postoperatively 78 survivors from a group of 96 surgical patients treated by saphenous vein coronary artery bypass graft surgery. In all 25 patients who were studied by bicycle ergometry, exercise performances increased, but the increase was smaller in patients with closed grafts.

Guiney et al.[14] described 38 survivors among 40 surgically treated patients who performed maximal exercise tests on a bicycle ergometer preoperatively and 3 to 8 months after coronary bypass graft surgery. In 20 of these 38 patients (53 percent), neither angina nor ischemic S–T segment depression greater than or equal to 1 mm occurred when they exercised to fatigue. Another 10 patients (26 percent) experienced angina or greater than 1 mm ischemic S–T segment depression at a higher value for product of systolic blood pressure times heart rate.

Follow-Up Coronary Arteriography in Surgical Patients

Griffith et al.[20] pointed out that although 86 percent of their 71 patients had symptomatic relief of angina and 60 percent of these 71 patients had no angina after coronary artery saphenous vein bypass graft surgery, 50 of these 71 patients (70 percent) had occlusive changes in the intrinsic coronary arterial circulation 6.1 ± 0.8 months after operation.

Lespérance et al.[21] demonstrated that 133 of 154 (86 percent) coronary artery saphenous vein grafts were patent at 2 weeks after operation and that 103 of these 154 grafts (67 percent) were patent at 1 year. Alderman et al.[12] evaluated graft patency in 63 of their 93 one-year survivors at an average period of 11.5 months after operation. Eighty of the 106 grafts (75 percent) in these 63 patients were patent.

From a group of 96 patients with angina treated by saphenous vein coronary artery bypass graft surgery, 78 survivors were restudied 12 to 28 months postoperatively by Miller et al.[19] They found that in these 78 patients all grafts were patent in 52 (67 percent), all grafts were closed in 6 (8 percent) and one or more grafts were closed in 20 (25 percent). Griffith et al.[20] found that 79 of 120 saphenous vein coronary artery bypass grafts (66 percent) placed in 71 patients were patent 6.1 ± 0.8 months after operation. We found in our study that 18 of 27 grafts (67 percent) in 18 patients were patent 1 year after operation.

Mechanisms for Postoperative Improvement

Improvement in exercise performance and reduction of postexercise ischemic S–T segment depression after coronary artery bypass graft surgery has been attributed to improved coronary blood flow. However, all three of our patients who had operative myocardial infarction had no anginal pain or electrocardiographic evidence of myocardial ischemia after exercise in their postoperative studies. We agree with Brewer et al.[16] that one must consider at least four possible mechanisms causing alleviation of angina after coronary artery bypass graft surgery. These are (1) increased coronary blood flow to ischemic areas of myocardium, (2) placebo effect, (3) necrosis of ischemic areas of myocardium, and (4) interruption of afferent nerve fibers for pain.

Clinical Implications

In conclusion, there is no good evidence that coronary artery bypass graft surgery favorably alters the natural history of stable angina pectoris due to coronary artery disease in comparison with medical therapy by reducing mortality or preventing myocardial infarction. The operation may, however, improve the quality of life in many surviving patients with angina. On the basis of a critical review of the literature and our data, we believe that coronary artery bypass graft surgery should be considered in patients with disabling stable angina despite appropriate medical therapy who have coronary angiographic evidence of a significant bypassable lesion with good patent distal runoff. This operation should not be performed in asymptomatic persons or in patients with stable angina who respond well to medical management.

Acknowledgment

We gratefully acknowledge the many physicians, especially John C. Kern, MD, who assisted in performing this study, the technical assistance of Michael W. Isbell, CPT, and the help of Reed Boswell, PhD, for biostatistical analysis of the data.

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Symposium on the Effects of Surgical Treatment on the Natural History of Acquired Heart Disease. Part I. Coronary Artery Disease

JOHN ROSS, Jr., MD, FACC, *Guest Editor*

Introduction

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This Symposium grew directly out of a session of the same title held at the Annual Meeting of the American College of Cardiology on February 16, 1973. The theme was simple: What are the immediate and late risks to life of nonoperative treatment versus operative intervention in patients with cardiac disease, and what are the chances of significantly altering the quality of life or arresting progression of disease? To answer these two questions in a rational manner, both the natural history of disease and the early and late effects of operative treatment must be known. The key problem has been to have such information in matched groups of patients whose condition has been carefully characterized by cardiac catheterization, angiography and other objective methods. Only in recent years have some prospective studies of natural history in such patients become available, and even after many years of technically sound operative treatment there continues to be inadequate prospective information on postoperative history.[1] The Symposium was designed to focus attention on these problems, with Dr. T. Joseph Reeves discussing the natural history of patients with coronary heart disease for comparison with results of coronary revascularization procedures, reviewed by Dr. Vincent L. Gott (Part I of the Symposium). Dr. Elliot Rapaport then analyzed the natural history of patients with various forms of valvular heart disease, and Dr. Dwight C. McGoon compared these findings with the course after surgical treatment by prosthetic valve replacement (Part II of the Symposium, to be published).

In discussing the natural history of patients with coronary heart disease, Reeves and co-workers provide a comprehensive historical review and a contemporary analysis of risk factors that has considerable pertinence to studies on the natural history of all types of heart disease. They point out the serious problems in early studies of patients who died from heart disease, emphasizing that unless an entire cohort of subjects is followed up until death the term "average survival" means little. They further point out the need to make comparisons in similar populations; for instance, differences in survival statistics in two populations that are not age-matched may disappear if the data are adjusted for survival rates of the normal population at the same age. Reeves et al. then focus on the prognostic implications of specific risk factors. Thus, whereas the Framingham Study indicates that the annual mortality rate is about 4 percent in an unselected population with angina pectoris,[2] when both hypertension and electrocardiographic changes are also present the risk is many times greater. Perhaps even more important is the extent of coronary artery involvement. Recent studies demonstrating a relation between the extent of coronary artery disease (as revealed by coronary arteriographic findings) and prognosis are reviewed. Data available so far in such prospective studies show an average annual mortality rate of 2.2 percent in patients with single vessel coronary artery disease, 6.8 percent in those with double vessel disease and 11.4 percent in patients with triple vessel disease. These average figures accord remarkably well with those recently reported by Bruschke et al.[3] in patients who were not treated surgically at the Cleveland Clinic.

Reeves and co-workers also analyze an additional important risk factor in the prognosis of such patients: the degree of myocardial involvement. In their data, mortality was increased threefold if clinical symptoms of left ventricular failure were present in patients with two or three vessel coronary artery disease, and if heart volume (calculated by plain roentgenography) was enlarged, patients with two vessel disease had six times the mortality rate of those with a normal heart volume. These data conform to our recent finding[4] that patients followed up prospectively after acute myocardial infarction have approximately a fivefold increase in mortality if left ventricular size is increased. The need for this type of information in studies on natural history and postoperative course in patients with valvular heart disease seems clear.

In analyzing the outlook for patients after coronary artery revascularization, Gott reviews surgical results from various centers, focusing on survival statistics as well as on relief of symptoms. It seems evident that

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myocardial revascularization in the patient with uncomplicated stable angina pectoris can now be accomplished with a relatively low operative mortality rate (average less than 6 percent). Perhaps the most promising preliminary study so far is that of Sheldon et al.,[5] which suggests that overall annual mortality rates in patients after operation are lower than in patients treated medically. They report an average annual mortality rate of only 4.1 percent (including hospital mortality) over a relatively short average follow-up period (22 to 60 months), which is clearly lower than that in patients with multivessel disease who have not been treated surgically. However, more data in this area are necessary. Gott's analysis also draws attention to the fact that more than 80 percent of patients manifest symptomatic improvement after bypass operations, and that objective measures of improvement (coronary arteriography, treadmill testing, for example) generally correlate with and corroborate such symptomatic improvement.

The special problem of unstable angina pectoris is now the object of at least two prospective, randomized studies (Veterans Administration Cooperative and Myocardial Infarction Research Unit studies). As Gott points out, problems in defining this entity and in follow-up have resulted in reported first year mortality rates ranging between 3 and 43 percent. He also briefly discusses the experimental nature of coronary revascularization early after acute myocardial infarction and in the treatment of patients with cardiogenic shock. Recent experimental studies indicate the feasibility of salvaging myocardial tissue by revascularization within a few hours of an acute coronary occlusion,[6] and it has been shown that experimental infarct size can be reduced by pharmacologic and other therapeutic means.[7] Thus, in the future, reduction of infarct size may also become an important consideration in assessing the effects of emergency medical and surgical interventions in man.

It may be hoped that placing the natural history side by side with the course of disease after cardiac surgical treatment in patients whose condition has been objectively characterized will lead to increased appreciation of the need for more prospective analyses of this type. Ultimately, such information will allow the decision of whether or not, or when, to operate on the individual patient with cardiac disease to be made on a more rational basis. Such objective data also may eventually elucidate such unknown factors as the rate of progression of coronary atherosclerosis both with and without surgical intervention and the question of whether chronic myocardial dysfunction can be reversed after cardiac operations. Although some studies in patients with valvular[8] or coronary heart disease[9] suggest that it cannot be reversed, additional prospective investigations may allow a definite answer to this important question.

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Natural History of Angina Pectoris

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An understanding of the natural history of angina pectoris is crucial to decision making in the management of patients with this disease. Early investigations suggested a highly variable annual mortality rate, ranging from 2.5 to 9 percent. These studies clearly pointed to the association of certain electrocardiographic changes, hypertension, cardiac enlargement and congestive heart failure with increased mortality. Several recent studies based on findings at coronary arteriography indicate a high degree of correlation between the extent of coronary atherosclerotic occlusive disease and the likelihood of early death. A combination of data from several laboratories indicates that if only one of the three major coronary arterial branches (left anterior descending, left circumflex or right) is significantly stenosed, the annual mortality rate will be approximately 2 percent of the cohort. If two of the three major arteries are stenosed, the rate will be approximately 7 percent, and if all three arteries are stenosed, it will be approximately 11 percent. Some data suggest that these mortality figures based on the extent of atherosclerotic occlusive disease are importantly modulated by the extent of ventricular myocardial impairment as reflected by cardiac enlargement or symptoms of congestive heart failure.

According to William Heberden's original description of angina pectoris in the 18th century, "The termination of the angina pectoris is remarkable. For if no accident intervenes but the disease goes on to its height, the patients all suddenly fall down and perish almost immediately."[1] Fear of this sudden and premature death now provides the great impetus for coronary arteriography and bypass surgery that characterizes the practice of cardiology in 1974. In this review we examine the basis for this fear in a consideration of what is known of the natural history of the disease.

Survival Studies in the Pre-Coronary Arteriography Era

The early pessimism of Heberden was shared and augmented by the great cardiologists of the early 20th century whose estimates of the prognosis of the disease were based on duration of life of relatively small numbers of patients followed up until death (Table I).[2–7] Herrick and Nuzum[2] in 1918 reported an average survival period of only 3 years in 50 fatal cases from a total series of 200 patients with angina pectoris. In 1923 Sir James Mackenzie[3] reported an average survival period of 5.4 years in 214 fatal cases in a cohort of 380 patients with angina pectoris. In 1926 Paul Dudley White[4] reported his observations on a series of 200 patients studied from 1920 to 1926, noting an average survival of 3.4 years in the 66 patients who had died. Importantly, he also paid attention to the survival period of the 134 patients still alive, which was then 4.6 years. Subsequently, White with Bland[5] added 300 more patients, making a total of 500 patients entered into the study between 1920 and 1931. No other new

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This work was supported in part by U. S. Public Health Service Grant 5-P01 HE11310-06 and U. S. Social and Rehabilitation Service Grant 13-P-55477/4-01.
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TABLE I

Survival of Patients with Angina Pectoris: Early Studies

Author	Year	Surviving Patients (no.)	Years from Onset to Death (average)
Herrick and Nuzum[2]	1918	50	3
Mackenzie[3]	1923	214	5.4
White[4]	1926	66	3.4
White and Bland[5]	1931	213	4.4
White et al.[6]	1943	445	7.9
Richards et al.[7]	1956	456	9.7

TABLE II

Survival of Patients with Angina Pectoris: Later Studies

Author	Year	Cases (no.)	Survival Rate (%) 1 Year	5 Years	10 Years
Sigler[8]	1951	1,700	...	33	10
Block et al.[9]	1952	6,882	85	58	33
Richards et al.[7]	1956	500	...	75	59
Zukel et al.[10]	1969	690	98	90	75
Kannel and Feinleib[11]	1972	303	...	80	62

patients were added and all 500 patients were followed up until death or for 25 years; the completed study was reported by Richards, Bland and White in 1956[7] after an interim report issued in 1943.[6] As would be expected, the average survival period (onset of angina to death) in the fatal cases gradually increased to 9.4 years as the study continued. On its completion in 1956, 445 of the patients were dead, 6 were living and 5 lost to follow-up study. The other 47 patients had been reclassified because of associated valvular or aortic disease. Among the six living patients, the average survival was 31.7 years after diagnosis. It is now generally appreciated that unless the entire cohort of subjects is followed up until death the term "average survival" is without significance.

Figure 1 shows the survival curves for the 451 patients in White's study who were completely followed up. For both male and female subjects the curves are almost linear for the first 20 years. Thus, at 5.5 years, 25 percent of the male and 17 percent of the female subjects were dead, and at 10.5 years, 41 percent of the male and 39 percent of the female subjects were dead. The annual mortality rate of the entire cohort was slightly more than 4 percent.

Table II presents the survival rates of patients in several long-term follow-up studies.[6,8–11] These data indicate a variable prognosis, ranging from a 10 percent 10 year survival rate in a study reported by Sigler[8] in 1951 to a 75 percent 10 year survival rate in a study of young army men by Zukel et al.[9] Block et al.[9] of the Mayo Clinic reported a massive study involving 6,882 patients in which survivors were followed up for a minimum of 5 years. Their 5 year survival rate was 58 percent and the 10 year survival rate 33 percent. The findings of White et al.[6] have already been discussed. Zukel et al.[10] reported a 2.5 percent annual mortality rate in a study of younger army men. Kannel and Feinleib[11] in the Framingham study reported statistics very similar to those of White and his colleagues, indicating an overall annual mortality rate of approximately 4 percent, with 62 percent surviving at 10 years.

The great variation in these studies has caused considerable confusion. Many of the differences are clearly related to differences in the populations studied. Sigler[8] included patients with acute myocardial infarction, and more than half (891 of 1,700) of his patients had a myocardial infarction as the first clinical manifestation of disease. The patients described by Block et al.[9] had been referred to a large diagnostic clinic; thus, their study clearly represents some measure of selectivity. The patients of Zukel et al.[10] not only were younger than those of the other investigators, but also were generally free of other major complicating diseases. The community study by Kannel and Feinleib[11] is perhaps more representative of the total population of patients with angina pectoris. In these early studies coronary arteriography was not performed, and the data reflect entire cohorts of patients with angina pectoris; that is, all potential subclasses have been grouped together.

Identification of high risk factors: It should not be inferred that these early investigators were not aware of the differences in survival rates of subclasses of patients with different characteristics. White and his colleagues[7] noted that women had a better prognosis than men and that patients with hypertension, cardiomegaly, congestive heart failure and certain electrocardiographic abnormalities had a much greater likelihood of early death than patients without such findings. Block et al.[9] also studied survival with respect to age and sex, hypertension, electrocardiographic abnormalities, cardiomegaly and congestive failure. As can be seen in Table III, ventricular

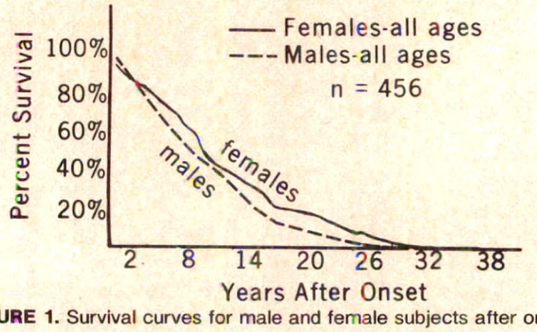

FIGURE 1. Survival curves for male and female subjects after onset of angina pectoris. (Redrawn by permission from Fig. 3, Richards et al.[7])

hypertrophy, even mild hypertension, congestive heart failure and electrocardiographic abnormalities all markedly diminished the survival rate of persons with coronary heart disease.

Block et al.[9] presented the survival curves as determined by an actuarial method for the male and female subjects of the study as contrasted to a normal population matched for age (Fig. 2). The better survival rates of female subjects are consistent with the earlier data of White et al.[7] and the recent findings of Kannel and Feinleib[11] in Framingham. Angiographic studies of patients with chest pain have consistently shown that a higher proportion of women than men have normal coronary arteriograms. This finding implies that woman may have a higher percentage of "false positive" clinical diagnoses of angina pectoris, a possibility that may explain this apparent sex difference. The question merits further study. In the study of Block et al.,[19] the 5 year survival rate of the age-matched normal population was 86.9 percent and the 10 year survival rate of their normal group was 70.4 percent. The older subjects with angina had a higher mortality rate than the younger ones. However, this difference was completely eliminated when survival rates were adjusted for the survival rates of normal subjects of the same age, thus indicating that increased age is not a specific added risk for patients with angina as compared to a normal population.

Weinblatt et al.[12] made an important study of angina in a defined population of white men between the ages of 25 and 64 years enrolled in a prepaid comprehensive group practice, The Health Insurance Plan of New York (HIP). This study, reported in 1968, differed from most others in that a defined population was studied prospectively, the subjects were all men under age 65 (mean age 55 years) and none had prior myocardial infarction or associated valvular heart disease. Particular attention was paid to the possibility of classifying these men with angina into high and low risk groups. There were 275 men with angina in the total cohort having a 10.5 percent mortality rate in 30 months of follow-up study, four times the rate of the age-matched persons in the total population at risk. A casual blood pressure determination at initial examination greater than 160 mm Hg systolic or greater than 95 diastolic was associated with a 30 month mortality rate of 18.6 percent compared to a 7.8 percent mortality rate in normotensive persons. In the 98 men whose electrocardiogram revealed a specified abnormality—usually a horizontal depression of the S–T segment of 0.5 mm or greater—the 30 month mortality rate was 20.8 percent as contrasted with 5.0 percent in 17 men with a normal electrocardiogram. In 30 men with both hypertension and electrocardiographic abnormalities, the mortality rate was 31.8 percent as contrasted to a 3.5 percent 30 month mortality rate in men with normal blood pressure and a normal electrocardiogram. The great significance of this study is its demonstration that with use of very simple and noninvasive measurements, persons with angina and at high risk of death can be separated from those with angina and a very low risk of death.

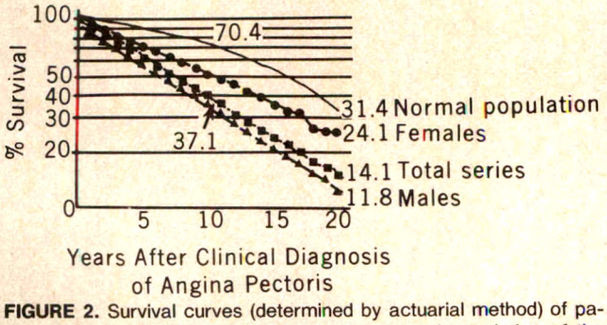

FIGURE 2. Survival curves (determined by actuarial method) of patients who had angina pectoris and of a normal population of the same age and sex consitution. (Redrawn by permission from Fig. 1, Block et al.[9])

TABLE III

Factors Affecting Survival of Patients with Angina Pectoris*

	Cases (no.)	5 Year Survival Rate (%)
Total cohort	5,766	58.4
Cardiac hypertrophy	1,619	41.4
Hypertension, class 2	647	46.1
Congestive failure	297	20.2
Normal electrocardiogram	978	73.1
Abnormal electrocardiogram (inverted T_1 and T_2)	423	29.1

* Data from Block et al.,[9] 1952.

Survival of Patients Studied by Coronary Arteriography

Johns Hopkins Study

In 1970 Friesinger et al.[13] of Johns Hopkins reported a very important investigation. Their study population consisted of 224 persons with chest pain studied by coronary arteriography and then followed for an average period of 50 months. The coronary arteriograms were scored as follows: For each of three major arterial branches—the right, left anterior descending and left circumflex arteries—a score of zero was assigned if no disease was recognized, 1 if trivial disease was present, 2 if the extent of stenosis was between 50 and 90 percent, 3 if multiple narrowings between 50 and 90 percent were present in a single artery, 4 if the stenosis was greater than 90 percent but there was less than complete obstruction, and 5 if the artery was completely occluded. If the arteriographic score was greater than 10, implying significant obstruction in at least two arteries, the mortality rate at 50 months was 53 percent, contrasted to 5 percent in those with a score greater than 3 but less than 10. Only 1 of 32 patients with single vessel disease died

TABLE IV

Mortality Rate of 246 Patients with Angina Pectoris According to Number of Coronary Arteries with Luminal Stenosis of 50 Percent or More*

Vessels Stenosed (no.)	Cases (no.)	Dead at 22 Months		Annual Mortality Rate (%) (original cohort)
		no.	%	
0	98	3	3	1.4
1	46	2	4	2.0
2	50	13	26	13.0
3	52	15	29	15.0

* Data from Oberman et al.[14] (1972): 194 men, 52 women aged 18 to 72 years (mean age 46.8 years).

TABLE V

Mortality Rate at 22 Months of 246 Patients with Angina Pectoris, According to Presence of Myocardial Infarction and Number of Coronary Arteries with Luminal Stenosis of 50 Percent or More*

Vessels Stenosed (no.)	With MI			Without MI		
	Cases (no.)	Dead (no.)	Mortality Rate (%)	Cases (no.)	Dead (no.)	Mortality Rate (%)
0	3	1	33	95	2	2
1	16	2	12.5	30	0	0
2	19	7	37	31	6	19
3	26	10	39	26	5	19
Total	64	20	31	182	13	7

* Data from Oberman et al.[14] (1972).
MI = myocardial infarction documented by electrocardiogram.

within the 50 month follow-up period, that patient dying in an automobile accident. Twenty-four of these patients had disease of the left anterior descending coronary artery, and in most the lesion was proximal to the first septal perforating branch.

University of Alabama Study

Oberman et al.[14] at the University of Alabama have also reported a follow-up study of persons with chest pain undergoing coronary arteriography. These investigators analyzed data from 246 patients studied by arteriography from July 1965 through June 1970. During that period coronary arteriograms were obtained in 437 patients. Associated cardiovascular disease such as aortic or mitral valve disease, overt cardiomyopathy, serious noncardiovascular disease or technically unsatisfactory arteriograms constituted causes for exclusion from the study. Of the remaining 304 patients, 55 underwent some form of cardiovascular surgical procedure, 2 were lost to follow-up study and 1 died immediately after coronary arteriography. The remaining 246 patients constitute the *study population*. It is relevant that this study was initiated before the advent of coronary artery bypass grafting at the University of Alabama; that is, the study population does not reflect preselection on the basis of current indications or contraindications for such surgery. The coronary arteriograms were scored according to the percent occlusion of each of the three major branches of the coronary arterial tree—the right coronary, the left anterior descending and left circumflex arteries. A vessel was considered "diseased" if the maximal obstruction was 50 percent or more of its lumen. Stenosis of the left main coronary artery was considered to represent two vessel disease.

As shown in Table IV, age at the time of the arteriogram ranged from 18 to 72 years (mean age 46.8 years) for 246 patients; 79 percent of all the patients were men. Ninety-eight patients had no diseased vessel; that is, no vessel was narrowed by 50 percent or more. Three of these patients died within the first 22 months of the follow-up study. Only one of these deaths—in a man with suspected cardiomyopathy—was cardiac in origin. Forty-six patients had single vessel disease, and two of these patients died in the follow-up period. Both had complete obstruction of the proximal left anterior descending coronary artery at the time of arteriography. Thirteen of 50 patients and 15 of 52 patients with two and three vessel disease, respectively, died in this period of 22 months. These data are in substantial agreement with those of Friesinger and co-workers[13] indicating that prognosis is closely related to the extent of arterial involvement, but additional important prognostic information was obtained from several of the other variables coded.

Electrocardiographic evidence of old transmural myocardial infarction was present in 64 patients with a 22 month mortality rate of 31 percent. In the 182 patients without this electrocardiographic abnormality, the mortality rate was only 7 percent. The difference in the mortality rate between those with and those without myocardial infarction is evident in all four classes of vessel disease (Table V).

A history of congestive heart failure, defined as dyspnea on effort plus either orthopnea or paroxysmal nocturnal dyspnea, was clearly related to prognosis. The 22 month mortality rate for the 45 patients with definite symptoms of pulmonary venous hypertension was 40 percent compared to 8 percent in the 201 patients without such symptoms. Of particular interest was the higher than 50 percent mortality rate in the 30 patients with either two or three vessel disease and congestive heart failure compared to the 16 percent mortality rate in similar patients without failure (Table VI).

Heart volume, as determined by measurements of standard posteroanterior and lateral chest X-ray films, was also significantly related to mortality in all classes of vascular involvement (Table VII). Thus, in patients with two vessel disease and a heart volume

TABLE VI

Mortality Rates at 22 Months of 246 Patients with Angina Pectoris, According to Symptoms of Congestive Heart Failure and Number of Coronary Arteries with Luminal Stenosis of 50 Percent or More†

Vessels Stenosed (no.)	Symptoms of Congestive Heart Failure			No Symptoms of Congestive Heart Failure		
	Dead (no.)	Alive (no.)	Mortality Rate (%)	Dead (no.)	Alive (no.)	Mortality Rate (%)
0	1	8	11	2	87	2
1	1	5	17	1	39	2.5
2	9	5	65	4	32	11
3	7	9	44	8	28	22
Total	18	27	40	15	186	8

* Data from Oberman et al.[14] (1972).

TABLE VII

Mortality Rate at 22 Months of 246 Patients with Angina Pectoris According to Heart Size and Number of Coronary Arteries with Luminal Stenosis of 50 Percent or More*

Vessels Stenosed (no.)	Heart Volume ≥396 cc/m²			Heart Volume <396 cc/m²		
	Dead (no.)	Alive (no.)	Mortality Rate (%)	Dead (no.)	Alive (no.)	Mortality Rate (%)
0	2	34	5.5	0	47	0
1	1	20	5	0	22	0
2	11	16	41	1	14	7
3	13	21	38	2	7	22
Total	27	91	23	3	90	3

* Data from Oberman et al.[14] (1972).

TABLE VIII

Mortality Rates of 200 Patients with Angina Pectoris, According to Number of Coronary Arteries with Luminal Stenosis of 50 Percent or More*

Vessels Stenosed (no.)	Cases (no.)	Dead at 7 Years		Annual Mortality Rate (%) (total cohort)
		no.	%	
1	84	10	20	3
LAD	36	11	20.5	4
RCA or LCA	48	6	12.5	2
2	82	36	44	6
3	34	24	70	10

* Data from Moberg et al.[15] (1972): Patients with congestiv heart failure, cardiomegaly or severe left ventricular dysfunctio were excluded.

LAD = left anterior descending coronary artery; LCA = le circumflex coronary artery; RCA = right coronary artery.

in excess of 396 ml/m², the 22 month mortality rate was 41 percent; in those with two vessel disease and a heart volume of less than 396 ml/m², the mortality rate was only 7 percent. Overall, the mortality rate for patients with a larger heart was 23 percent compared to only 3 percent in those with a smaller heart. The great majority of patients with two or three vessel disease had a heart volume greater than 396 ml/m² body surface area, which was the experimentally determined volume providing greatest separation between patients living and dying in the follow-up period. Several other factors, including S–T segment abnormalities, positive exercise tests and high resting heart rates, all had a significant association with prognosis.

Predictors of mortality: Many of the factors that correlated highly with mortality were strongly interrelated. Therefore, the important variables were considered simultaneously by means of discriminant function analysis to ascertain the best individual predictors of subsequent mortality. This analysis also allowed an adjustment for age and certain other variables. Seven factors contributed significantly to the prediction of mortality. Overall, the coefficient of determination was highly significant ($P < 0.0001$) with an r value of 0.6. In order of independent contribution, the variables were (1) heart size, (2) stenosis of the left anterior descending coronary artery, (3) dyspnea on effort and either paroxysmal nocturnal dyspnea or orthopnea, (4) heart rate, (5) stenosis of the left main coronary artery, (6) stenosis of the left circumflex artery, and (7) stenosis of the right coronary artery. Thus, increased heart size, symptoms of heart failure and tachycardia at rest all contributed independently to prognosis as did disease of each of the coronary arteries. The number of patients with stenosis of the left main coronary artery was small with respect to those with stenosis of the other arteries, possibly leading to an underestimate of its significance. Other measurements that by themselves had a strong association with subsequent mortalit —including electrocardiographic evidence of prio transmural infarction, the presence of classic angin pectoris, increased cholesterol concentrations an blood pressure—did not make independent contribu tions according to this discriminant function analy sis. It is possible that these variables exerted their in fluence on survival by affecting either the number o vessels involved, heart size, heart failure or hear rate.

It is also possible that other factors will becom significant as independent determinants of surviva as the study is extended in time. But at an averag follow-up period of 22 months, these are not eviden as independent determinants.

Other Studies Correlating Mortality and Coronary Arteriographic Data

Other investigators have reported powerful associ ations between prognosis of angina pectoris and the

number of coronary vessels involved. At the 1972 meeting of the American College of Cardiology, Moberg et al.[15] presented information on 200 patients studied by coronary arteriography and then followed up for 7 years or until death (Table VIII). Seventeen of 84 patients with one vessel disease were dead within 7 years, yielding an average mortality rate for the total group of 3 percent per year. However, the mortality rate of those patients with disease of the left anterior descending coronary artery was almost twice that of patients with disease of the right or left circumflex arteries. The mortality rate of the group with two vessel disease was 6 percent per year and that of patients with three vessel disease was 10 percent per year.

Lichtlen and Moccetti[16] of Zurich reported at the 1972 annual meeting of the American Heart Association a very similar experience in a series of 231 patients followed up for an average of 32.5 months (Table IX). Ten percent of their patients with one vessel disease and 18 percent and 34 percent, respectively, of those with two and three vessel disease died within the follow-up period. Again, patients with disease limited to the left anterior descending coronary artery had a higher mortality rate, 20 percent in 32.5 months. At the same meeting, Slagle et al.[17] of Duke University reported their experience with 94 patients followed up for an average period of 15 months after coronary arteriography (Table X). A more recent report[18] on 590 consecutive nonsurgical patients with coronary artery disease revealed a 5 year mortality rate of 17 percent for those with one vessel disease, whereas the rates of the patients with two and three vessel disease were 38 percent and 55 percent, respectively. These data are consistent with those of the other reports.

TABLE IX

Mortality Rates of 231 Patients with Angina Pectoris, According to Number of Coronary Arteries with Severe Luminal Stenosis*

Vessels Stenosed (no.)	Cases (no.)	Dead at 32.5 Months		Annual Mortality Rate (%) (total cohort)
		no.	%	
1	83	8	10	4
LAD	24	5	20	7
RCA	26	2	8	3
LCA	9	0	0	0
2	62	11	18	7
3	86	29	34	12.5

* Data from Lichtlen and Moccetti[16] (1972): 220 men, 11 women aged 50 years or more.

LAD = left anterior descending coronary artery; LCA = left circumflex coronary artery; RCA = right coronary artery.

TABLE X

Mortality Rates of 94 Patients with Angina Pectoris, According to Number of Coronary Arteries Stenosed*

Vessels Stenosed (no.)	Cases (no.)	Dead at 15 Months		Annual Mortality Rate (%) (original cohort)
		no.	%	
1	20	1	5	4
2	26	5	19	15
3	48	12	25	20

* Data from Slagle et al.[11] (1972).

Summary of Combined Studies

Recognizing the heterogeneity of the population groups resulting from differing referral patterns, variations in techniques and different periods of follow-up study, we have combined data from these several studies to provide a crude idea of the fate of a large number of patients studied at various centers. The variations are compensated for in part by providing the range of values and by deriving a weighted average mortality rate in which the mortality rate of each of the studies is weighted by the reciprocal of the variance. The standard error is also shown. Despite the inherent problems in such analysis, the pooled results are remarkably similar and provide additional insight into the likely survival rates of the several subgroups.

Single vs. multiple vessel involvement: This combination of studies provided a total of 265 patients with one vessel disease having an average follow-up period of approximately 47 months. The weighted average annual mortality rate of this combined group was 2.2 ± 0.4 percent (Table XIA). This value assumes a linear relation between the rate of death and the duration of follow-up study. The death rate applies only to the original cohort, not to the survivors at the start of each new year of the follow-up period.

A similar combination of reports (excluding the data of Friesinger et al.,[13] which provide no information on the number of patients with two or three vessel disease) yielded 220 patients with two vessel disease. Sixty-five (29.5 percent) were dead in an average follow-up period of 38 months. The weighted average mortality rate per year of the original cohort was 6.8 ± 0.7 percent (Table XIB). Seventy-nine of 220 (35.9 percent) of persons with three vessel disease were dead in an average 33 month follow-up period, yielding a weighted average annual mortality rate of 11.4 ± 0.9 percent of the original cohort (Table XIC).

These data from several centers show a clearly recognizable trend; that is, the mortality rate of patients with angina is strongly associated with the number of arteries involved. But there is one area of important disagreement. Moberg and his colleagues[15] and Lichtlen and Moccetti[16] found that patients with "single vessel" disease involving the left anterior descending coronary artery have a relatively serious prognosis,

the annual mortality rate being 4 percent and 7.4 percent in their respective series. In contrast, Ross et al.[19] reported only one death (possibly cardiac in origin) in 24 patients with disease of the left anterior descending artery in a follow-up period of 55 months. The reports of Oberman et al.[14] and Slagle et al.[17] did not provide a similar breakdown of data, although the gross mortality rate of the patients with single vessel disease in both studies was low. This question obviously requires further study. It seems clear from all reports that patients with disease limited to the circumflex or to the right coronary artery have an excellent prognosis over a period of 2 to 7 years. It is also clear that patients with all three major vessels involved have a high mortality rate, approximately 10 to 15 percent per year. In all classes of patients cardiac enlargement or congestive heart failure, or both, grossly diminishes the likelihood of survival.

Clinical and Surgical Implications

These considerations indicate that if meaningful comparisons are to be made between medically and surgically treated patients, a number of subgroups must be identified, even if a randomized trial can be completed successfully. At a minimum these subgroups should be based on the extent of obstructive disease of the coronary arteries, the presence or absence of cardiomegaly, and the presence or absence of congestive heart failure. A more sophisticated analysis of the coronary arteriograms would almost certainly increase the precision of delineation of subgroups. It is also likely that more elegant descriptors of the condition of the ventricles than cardiomegaly or symptoms of congestive heart failure would further increase the refinement of these subgroups, as indicated in a very recent report by Scanlon et al.[20] on accelerated angina pectoris. A direct comparison of the survival and clinical course of patients in such subgroups assigned at random to medical or surgical treatment is required if clear answers relative to the respective merits of medical and surgical interventions are to be provided. In the absence of such data, the physician must be guided by the information available to him. In view of the low annual mortality rate of patients with disease limited to the right or left circumflex artery, it is difficult to justify an operation that, while providing symptomatic relief, may accelerate the disease process in the native coronary circulation as recently reported by Griffith et al.[21] and Levine et al.[22] and has the other

TABLE XI

Mortality Rates of Patients with One, Two and Three Vessel Disease by Coronary Arteriography

Author	Cases (no.)	Dead (no.)	Average Follow-up Months*	Average Patient Months	Annual Mortality Rate (%)
A. One Vessel Disease					
Friesinger et al.,[13] 1970	32	1	54	1,728	0.7
Oberman et al.,[14] 1972	46	2	20	920	2.6
Moberg et al.,[15] 1972	84	17	84	7,056	2.9
Lichtlen and Moccetti,[16] 1972	83	8	32	2,656	3.6
Slagle et al.,[17] 1972	20	1	15	300	4.0
Total	265	29	48	12,660	2.2 ± 0.4†
B. Two Vessel Disease					
Oberman et al.,[14] 1972	50	13	22.7	1,135	13.7
Moberg et al.,[15] 1972	82	36	84.0	6,888	6.3
Lichtlen and Moccetti,[16] 1972	62	11	32.0	1,984	6.7
Slagle et al.,[17] 1972	26	5	15.0	390	15.4
Total	220	65	47*	10,397	6.8 ± 0.7†
C. Three Vessel Disease					
Oberman et al.,[14] 1972	52	14	19.3	1,003	16.7
Moberg et al.,[15] 1972	34	24	84.0	2,856	10.1
Lichtlen and Moccetti,[16] 1972	86	29	32.0	2,752	12.6
Slagle et al.,[17] 1972	48	12	15.0	720	20.0
Total	220	79	33.3*	7,331	11.4 ± 0.9†

* Average follow-up = total patient months/total number of patients in combined series.

† Weighted average of annual mortality rate and standard error of combined studies, where the mortality rate of each study is weighted by the reciprocal of the variance. The calculations used are: Mortality rate (r) = d/NT; variance of rate (V_r) = d (N − d)/N^3T^2; and weight (W) = $1/V_r$ where d = no. dead; N = no. exposed to death; and T = time interval in years. Weighted average mortality rate = Σ Wr/ΣW and standard error of rate = $1/\sqrt{\Sigma W}$.

disadvantages of surgery. These disadvantages include a significant risk of infarction at operation, a definite if small surgical mortality rate, considerable pain and discomfort and a substantial cost both in dollars and in medical manpower.

By contrast, patients with three vessel disease, having a very high annual mortality rate with medical treatment alone, might well benefit from a more aggressive attitude on the part of physicians. At present it is our policy to offer surgery to essentially all of these patients who are without contraindications, recognizing that surgical intervention has not been shown to prevent premature death. Patients with two vessel disease or with very proximal disease of the left anterior descending coronary artery constitute the most difficult problems with respect to surgical intervention. If there is evidence of ventricular dysfunction or cardiomegaly, either condition of mild or moderate degree, especially if there is significant limitation of ordinary activity because of angina, then surgery is advised. Unfortunately, the patients with a very large heart and severe congestive heart failure who are at great risk of death with medical treatment alone are also those with the greatest hazard at surgery. Thus, in many centers these patients are not considered to be surgical candidates unless the dysfunction is explained by focal disease of the myocardium, with other areas of the ventricle exhibiting vigorous contraction.

Acknowledgment

We are indebted to Malcolm E. Turner, PhD, for his valuable advice on the statistical analyses.

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Outlook for Patients After Coronary Artery Revascularization

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Data are now available from many centers on the results of the coronary artery bypass operation. Approximately 85 percent of the patients who survive the procedure experience relief of angina and 60 percent have no further chest pain. Similarly, 70 to 85 percent of the patients have improved results on objective testing, and this improvement seems to correlate fairly well with the patency of the bypass grafts. Data from various institutions on effects on ventricular function have not been consistent, but there is some evidence that myocardial contractility for segments with a patent graft can be improved, particularly when there is no infarction and the preoperative ventricular wall motion is moderately depressed.

The operative mortality rate for patients with stable angina is less than 6 percent in most centers and appears to be related to the quality of ventricular function. The mortality rate in patients with unstable angina is considerably higher in most institutions. Although vein patency is reduced to between 65 and 75 percent 1 year postoperatively, the occlusion rate over the next 2 years appears to be only 5 to 6 percent.

It is too early to state definitively whether surgery can prevent infarction in patients with stable or unstable angina. However, there is fairly good evidence that bypass surgery can prevent infarction if it is carried out within 4 hours after the onset of coronary occlusion.

The results from several centers suggest that bypass surgery may favorably influence the annual survival rate in patients with stable angina. There are not enough controlled data to say whether the procedure can extend life in patients with unstable angina, which is a highly lethal disease, particularly for individuals with continuing severe angina. Bypass surgery would appear to be of value for this group of patients.

During the past 6 years, the coronary artery bypass operation has been widely used as a myocardial revascularization procedure in many cardiac centers. Thousands of patients have been subjected to this operation, and it is important at this time to determine how beneficial the procedure has been. Has it been of value in eliminating the symptoms of angina? Has there been demonstrated improvement in ventricular function? More important, has it reduced the frequency of infarction and extended life in these patients? There is now a considerable amount of data to help formulate answers to these questions.

Vein Patency Rate and Mortality Rate After the Bypass Operation

Before considering the possible benefits of the newer bypass procedures, it is important to consider: (1) the percentage of bypass grafts that will remain open over a prolonged period of time, and (2) the mortality rate of the operative procedure.

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Vein Patency Rate

Several institutions have reported early patency rates of 85 to 92 percent 2 to 3 weeks after operation, and reports by Achuff et al.[1] at our institution and Walker[2] and Grondin[3] and their co-workers have demonstrated late patency rates of 65 to 75 percent 4 to 12 months after operation. One of the best studies on the late patency rate was recently reported by Grondin et al.[4] from the Montreal Heart Clinic. They demonstrated, in a serial angiographic evaluation of vein bypass grafts in 60 patients, patency rates of 89 percent 2 weeks after operation and 68 and 63 percent 1 year and 3 years, respectively, after operation. It is gratifying that the reduction in patency between the first and third years was only 5 percent.

Several factors appear to affect the patency rate. Possibly the most important is the severity of obstructive disease in the distal arterial bed and the amount of blood flow or "runoff" that can be accepted by this bed after the graft placement. Grafts with flow rates of less than 20 cc/min have a very high frequency of early closure. Grafts with flow rates of more than 40 cc/ min have an excellent late patency rate.[2,5]

The results with the internal mammary artery as a bypass conduit have been more encouraging, demonstrating a 90 to 95 percent patency rate 1 year postoperatively.[6] This high patency rate has increased interest in use of the internal mammary artery as a bypass conduit for the left anterior descending and the circumflex coronary arteries. Ordinarily, the internal mammary artery is not of adequate length to reach the distal right coronary arterial tree.

TABLE I

Mortality Rate for Coronary Bypass Operation in Patients with Stable Angina

Study	Patients (no.)	Mortality Rate (%)
Anderson et al.[7]	141	6.0
Alderman et al.[8]	102	3.9
Sheldon et al.[9]	1000	4.0
Reul et al.[10]	759	4.5
Johns Hopkins	170	4.7

TABLE II

Importance of Left Ventricular Function in Determining Mortality Rate*

Patients (no.)	Left Ventricular Ejection Fraction	Mortality Rate (%)
529	0.45–0.70	3
232	0.25–0.40	6
78	<0.20	31

* Adapted from Kay et al.[11]

TABLE III

Symptomatic Improvement After Coronary Artery Bypass

Study	Patients (no.)	Improved (%)	Angina-Free (%)
Collins et al.[12]	116		71
Anderson et al.[7]	200	89	
Cooley et al.[13]	1105	94	62
Achuff et al.[1]	71	86	60
Miller et al.[14]	98		72
Bartel et al.[15]	92		70
Matloff et al.[16]	71	80	65

Mortality

The risk of operation in patients with stable angina pectoris appears to be less than 6 percent. Table I[1–10] presents the mortality rate for several large series of patients with stable angina. Probably the most important factor in determining the mortality rate in patients with stable angina is the degree of left ventricular malfunction. This is well illustrated by the data reported by Kay et al.[11] (Table II). In their study, mortality rate was related to left ventricular ejection fraction, and very acceptable mortality rates were achieved even with only fair ventricular function. When the ejection fraction was under 20 percent, however, the mortality rate increased to 31 percent.

Clinical Results of Bypass Operation

Symptomatic Improvement

Probably the most significant benefit of the coronary bypass operation at this time is the symptomatic relief of angina pectoris. Table III shows the close relation of the data reported from seven different institutions.[1,7,12–16] Eighty to 95 percent of the patients had symptomatic improvement after the bypass operation, and 60 to 72 percent were angina-free. Therefore, for approximately 65 to 85 percent of the patients who survived this operation, the "quality of life" has improved significantly. Most of these patients have been able to return to work and, from the standpoint of the patient, the operation has been highly successful.

Objective Improvement by Stress Testing

Results of the data becoming available on the objective improvement in patients who have survived the bypass operation are quite encouraging. Table IV presents data from several studies[1,15,17–19] on the objective improvement as determined by stress testing, with right atrial pacing-induced tachycardia or exercise. It is apparent that 64 to 86 percent of these patients showed improved performance after the bypass operation.

Thus, approximately 85 percent of patients appear to have symptomatic improvement after the bypass operation, and approximately 80 percent improvement by objective measurements. Physicians tend to

be skeptical of these data because very similar benefits were reported after internal mammary artery implantation (Vineberg procedure), even when it was demonstrated that there was an occluded internal mammary artery implant. Several studies have shown that approximately 35 percent of patients who had an occluded internal mammary artery had symptomatic improvement and that many of these patients also demonstrated objective improvement. There is a real placebo effect, therefore, from any of the so-called revascularization operations, and physicians must remain cautious in interpreting these new data on symptomatic and objective improvement after the bypass operation.

It has been encouraging to note that there appears to be a fairly good correlation between the presence of a patent bypass graft and the degree of postoperative symptomatic and objective improvement. Also, several groups have noted a good correlation between the return of symptoms and occlusion of the grafts. Experiences of this type indicate that increased myocardial perfusion is very likely responsible for the reduction in symptoms in many patients undergoing the bypass operation. Alleviation of the symptomatic complaints of angina can, of course, also be related to postoperative infarction. This was well documented in a study by Griffith et al.[20] in which 56 of 71 patients undergoing vein bypass surgery reported symptomatic improvement, and in at least 9 of these 56 patients, improvement was apparently the result of a postoperative infarction.

Improvement in Ventricular Function

A more critical assessment of the value of the vein bypass procedure can be obtained by actually determining the improvement in left ventricular function after surgery. However, current data are inconclusive. The majority of patients undergo vein bypass operation for incapacitating angina, and if they have essentially normal left ventricular function, it will not be improved by the bypass procedure. In other words, one cannot expect "supercontraction" of a normal ventricle with the placement of a vein bypass graft. Also, in patients who have had a myocardial infarction, one cannot expect improvement in the contraction of scar tissue. The hope is that the patient with poor left ventricular function on the basis of ischemia will demonstrate improved function after the bypass operation.

Data presented in Table V have been abstracted from several reports and are not uniform or consistent with regard to the improvement in left ventricular function after the bypass operation. Achuff et al.[21] at our institution, in evaluating 71 patients after vein bypass surgery, found essentially no improvement in ventricular function as determined by left ventricular ejection fraction. It made very little difference if the veins were open or occluded. They did find that 26 percent of the ventricular segments demonstrated improved wall motion when bypass grafts to these segments were patent, but the improvement was not impressive when they evaluated changes in all myocardial segments.

Arbogast et al.[22] reported that the ejection fraction in 23 patients with all grafts patent was unchanged, whereas it was definitely worse in 19 patients with all grafts occluded. Rees and associates[23] similarly found poor ventricular wall motion in six patients with occlusion of all grafts. They indicated, however, that in eight patients with patency of all grafts, the ejection fraction and ventricular wall motion were better. They concluded that patients with severe depression of ventricular performance manifested improved ventricular function when the operation was a success and that a deterioration of ventricular function accompanied graft occlusion.

Chatterjee and associates[24] obtained results somewhat similar to those of Rees et al., in that they observed improvement in ejection fraction in 17 of 18 patients with moderate preoperative depression of left ventricular function and postoperative patency of all grafts. In three patients with occlusion of all grafts, ventricular function was further depressed. These latter two studies were somewhat selective with regard to the patients evaluated and the first

TABLE IV

Objective Improvement by Stress Testing After Coronary Artery Bypass

Study	Patients (no.) Total	Patients (no.) With Improved Performance	Interval After Surgery (mo.)
Bergman et al.[7]	20	14 (70%)	3.5
Achuff et al.[2]	65	56 (86%)	6
Bartel et al.[15]	92	59 (64%)	2–20
Guiney et al.[18]	38	30 (79%)	3–8
Manley et al.[19]	22	17 (77%)	12

TABLE V

Changes in Ventricular Function After Coronary Artery Bypass

Author and Number of Cases	Graft Status	Ejection Fraction	Comment
Achuff et al.[21]			
71		→	26% of ventricular segment improved with open graft
Arbogast et al.[22]			
23	Open	→	...
19	Closed	↓	...
Rees et al.[23]			
8	Open	↑	Selective group
6	Closed	↓	
Chatterjee et al.[24]			
18	Open	↑*	Selective group
3	Closed	↓	

* In 17 patients.

Arrows indicate improved (↑), worsened (↓) or unchanged (→) ejection fraction.

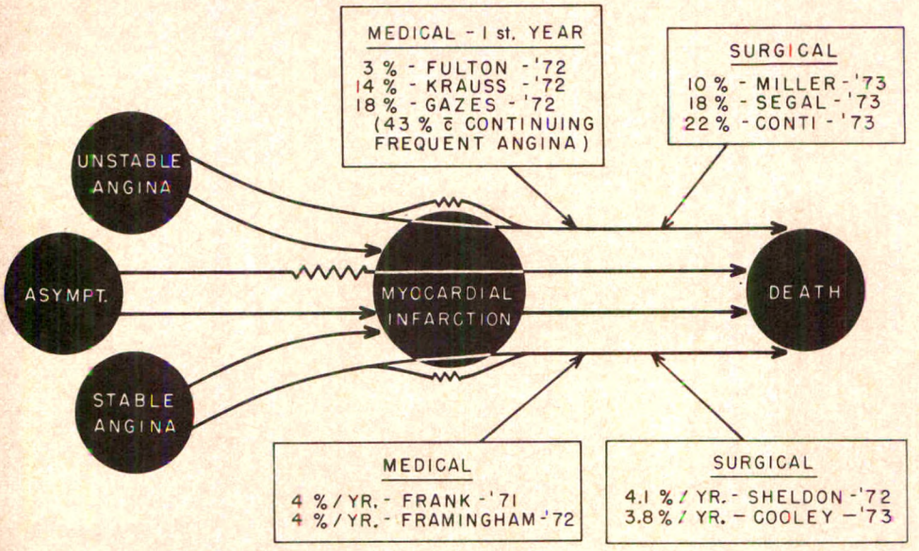

FIGURE 1. Schematic portrayal of three categories of patients who may experience myocardial infarction or progression to death as a result of infarction or electrical instability (wavy line). The mortality rates for each therapeutic group are depicted. A-SYMPT. = asymptomatic.

two groups (Achuff et al. and Arbogast et al.) were completely unselective. Thus, there is some evidence that, with moderate preoperative depression of ventricular function and postoperative graft patency, ventricular function in some patients can be improved, although this finding has not been uniform.

Extension of Life and Prevention of Myocardial Infarction

Reeves and associates[25] have provided an excellent discussion on the natural history of coronary disease, and it is important now to see if the bypass operation can alter this natural history. Figure 1 depicts in a highly schematic way the various interrelations among the clinical presentations of ischemic heart disease. This diagram simply depicts three categories of patients whose clinical course is characterized by development of myocardial infarction or by progression to death as a result of infarction or electrical instability. These three categories include asymptomatic patients and patients with stable or unstable angina. There is an additional subset of patients who do not undergo sudden death but are admitted to a coronary care unit with a potentially lethal myocardial infarction for which there is an interval of time for treatment.

Surgery has no current role in preventing infarction or sudden death in the asymptomatic patient without documented coronary artery disease. We are primarily concerned, therefore, about the possible role that surgery may have in altering the natural history pathways for patients with stable and unstable angina.

Patients with Stable Angina

Annual mortality rate: In studies made 10 to 15 years ago, the annual mortality rate in patients with stable angina was reported to be 8 to 9 percent.[26,27] More recently, there have been some excellent prospective studies on the yearly attrition rate in patients with stable angina. Two very good clinical studies are those generated by the Framingham group[28] and the Health Insurance Plan of New York (HIP).[29] In the HIP study, as reported by Frank,[29] there was a 4 percent annual attrition rate in men who had survived their initial coronary attack. Data from the Framingham study[28] demonstrated a comparable yearly attrition rate. It is important to note that Frank and his associates have reported an annual mortality rate of 8 percent in a high-risk group of men with an abnormal electrocardiogram and hypertension. In this same study, the annual attrition rate in a low-risk group of men with stable angina (normal electrocardiogram and normal blood pressure) was only 1.8 percent a year.

The two studies cited provide excellent clinical information on the natural history of patients with stable angina, but angiographic documentation of the severity of coronary artery disease was not obtained. Three important studies published in the last 2 years do provide excellent data on angiographic correlation with the annual mortality rate in patients with one, two and three vessel disease (Fig. 2). Friesinger et al.[30] of our institution reported in 1971 the results of a natural history study in which the severity of coronary disease had been initially documented by arteriography in 224 patients. All of these patients were then followed up for at least 5 years. It was found that patients with severe disease in at least two coronary arteries had an annual mortality rate of 10 percent (Fig. 2), and patients with less severe disease had an annual attrition rate of only 1 percent. This study was the first to show that the major determinant of survival in patients with angina pectoris was the severity of the coronary artery disease. A subsequent report by Jones et al.[31] has confirmed the important relation between the severity of the disease and patient survival. These investigators reported a

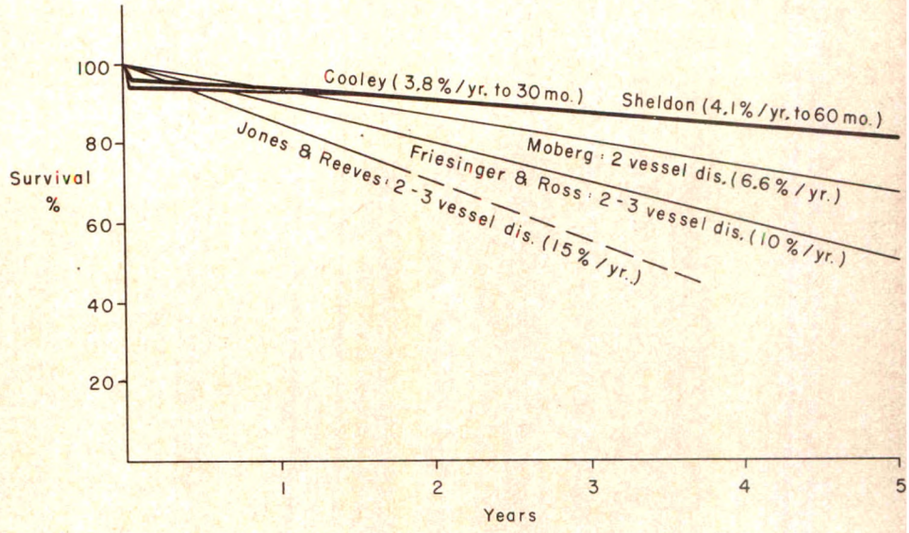

FIGURE 2. The annual attrition rate for patients with coronary disease documented by arteriography. The top line depicts data for patients undergoing coronary artery bypass in two different institutions. The lower three lines depict data from three studies in which revascularization was not carried out. Reprinted by permission from Gott VL, Brawley RK, Donahoo JS, et al: Current surgical approach to ischemic heart disease. In, Current Problems in Surgery, May 1973, p 1–53. Copyright © 1973 by Year Book Medical Publishers.

15 percent annual attrition rate in patients with severe disease in at least two coronary arteries. These data have now been further amplified by Reeves and associates[25] in their current presentation on the natural history of coronary artery disease. Moberg et al.[32] at the Cleveland Clinic more recently reported a 6.6 percent yearly attrition rate in patients with two vessel disease and a 4 percent yearly attrition rate in patients with single vessel disease.

Recent data based on evaluation of patients undergoing coronary artery bypass suggest that operation may favorably influence mortality in patients with stable angina (Fig. 1 and 2). In two groups of patients who underwent coronary artery bypass,[9,13] the annual attrition rates (including hospital mortality) were, respectively, 3.8 and 4.1 percent. Although all of the patients cited in Figure 2 had the severity of their coronary disease documented angiographically and the majority in the surgical series had severe two vessel disease, comparison of the survival rates of patients treated medically and surgically may be misleading. The results in the three groups of patients who received medical treatment were obtained during a period when some forms of current medical therapy were not available. In addition, it is not possible to determine how many patients in the group receiving only medical therapy would be suitable candidates for bypass graft surgery. Because patients with diffuse coronary disease and poor left ventricular function are often not selected for surgery, the medical group may include a significant number of patients with more advanced disease. In spite of these reservations, the data do suggest that the annual attrition rate of patients with stable angina can be favorably altered by the bypass operation.

Prevention of future myocardial infarction: Can the coronary artery bypass operation prevent future myocardial infarction? Unfortunately, there are not enough firm data to answer this major question. One problem has been obtaining accurate data on the annual incidence of nonfatal infarction in patients with stable angina on medical therapy. There is not much information in this area, but the Framingham study[28] indicated that 2 to 3 percent of patients with stable angina experience a nonfatal infarction each year. There are no comparable data for a group of patients with stable angina who have undergone bypass surgery. It can be said that the frequency of perioperative myocardial infarction, as defined by the appearance of new Q waves on the postoperative electrocardiogram, ranges from 2 to 22 percent in various reported series.[33–36] Although this is a relatively high rate, most infarctions occurred in the early postoperative period when appropriate therapy could be immediately employed. Perhaps the availability of immediate therapy explains why most of these early postoperative infarcts are not fatal. The incidence of late infarction (after hospital discharge) in patients undergoing successful coronary artery bypass operations appears to be low. In our first 141 patients discharged from the hospital and followed up for an average of 8.3 months, there were only six myocardial infarctions, one fatal and five nonfatal.

Currently, the Veterans Administration Hospitals (V. A. Cooperative Study of Surgery for Coronary Arterial Disease) are conducting an important prospective study to determine the effect of coronary artery bypass on the natural history of patients with ischemic heart disease. In that study, patients with disabling angina who are suitable candidates for bypass surgery are randomly assigned to either medical or surgical therapy. It is hoped that the data will provide some of the answers currently being sought. It is apparent that it will be several more years before we will know with certainty whether bypass surgery can reduce the incidence of myocardial infarction and improve the survival rate in patients with stable angina.

Patients with Unstable Angina

At the present time, probably no group of patients with coronary artery disease poses more of a therapeutic dilemma than the group with unstable or "preinfarction" angina. Evaluation of this problem is complicated by the fact that the terminology related to this clinical state has not been well defined, and frequently physicians, in comparing their experience with unstable angina, have not been describing comparable patient populations. As indicated in Figure 1, the reported first year mortality rate for patients with unstable angina has varied greatly (3 to 43 percent). Fulton et al.,[37] in reporting a 3 percent mortality rate within the first year after the onset of unstable angina, probably obtained this low rate because of the inclusion of a large number of patients with the recent onset of exertional angina. The patients in the studies of Krauss and Gazes and their co-workers[38,39] had a more lethal disease process and the criteria for unstable angina in these two studies are more comparable to those employed in the surgical groups presented in Figure 1.[40–42] In all of these medical and surgical studies (with the exception of that of Fulton et al.), the patients had as a minimal requirement at least a 15 minute episode of new, continuing angina of sufficient severity to warrant admission to a coronary care unit. The mortality for bypass surgery in patients with unstable angina varies considerably, with several factors affecting these results. In the series of Conti et al.,[42] for example, 40 patients with unstable angina were submitted to surgery with three of the nine nonsurvivors sustaining a cardiac arrest even before cardiopulmonary bypass could be instituted.

There is not sufficient evidence to determine whether surgery during an episode of acute coronary insufficiency or unstable angina is the most ideal method of therapy. Gazes et al.[39] have reported a 43 percent first year mortality rate in patients with unstable angina persisting for more than a few days, and bypass surgery certainly should be of value for this group. Krauss et al.,[38] however, raise an important question concerning the most opportune time for bypass operation in these patients. They report the follow-up data on 100 patients with unstable angina admitted to the coronary care unit at Massachusetts General Hospital. Only one patient died and six patients experienced acute infarction during hospitalization, but 26 late deaths occurred in patients discharged from the hospital (mean follow-up time 20 months). There was, therefore, a very high mortality rate in this group of 100 patients with unstable angina, but since there was only one death during the actual hospitalization, the authors suggest that initial conservative management should be considered for the acute syndrome except when the patient is experiencing persistent coronary pain after hospitalization.

These data emphasize the high risk of death in patients with unstable angina and suggest that bypass surgery probably would be of value if applied at the correct time. Currently, there is a prospective, randomized study of patients with unstable angina at eight institutions under the sponsorship of the Myocardial Infarction Branch of the National Heart and Lung Institute. Patients with unstable angina who enter the coronary care unit of a participating institution undergo cardiac catheterization. If they are suitable for vein bypass surgery, a card is drawn to select either medical or surgical therapy. This therapy is carried out and the patient is followed up closely for 24 months with electrocardiograms and chest roentgenograms at 3 month intervals.

In summary, there are considerable data available regarding the problem of unstable angina, and it appears that we can now better define a subset of patients who are at high risk of developing an infarction or dying. Many of these patients should benefit from a bypass operation carried out at the appropriate time. The prospective, randomized study underway at eight institutions may provide data within the near future as to the best time to proceed with bypass surgery.

Patients with an Acute Evolving Infarction

Although the bypass operation has been carried out in a few patients with acute evolving infarctions and also in a few additional patients with cardiogenic shock who were supported by aortic balloon augmentation during catheterization procedures, the role of surgery in these patients must be considered experimental at this time. If bypass surgery can be carried out within 4 hours of onset of a coronary occlusion, there may be some reversal of the periinfarction ischemic process. The few reports of bypass surgery in patients with early, acute evolving infarcts are fairly encouraging.[43,44] The results of vein bypass surgery for patients with cardiogenic shock provide less cause for optimism. However, there do appear to be some patients with cardiogenic shock who can be successfully supported during coronary angiography and bypass surgery with the aortic balloon augmentation system.[45] Although the overall survival rate in this group is low, each survivor represents the successful reversal of an almost certain fatal clinical course. It is important, therefore, that efforts be continued to utilize cardiovascular support techniques and coronary bypass procedures for this group of patients with cardiogenic shock.

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Echocardiographic Features of Primary Pulmonary Hypertension

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Echocardiograms were recorded in nine patients with primary pulmonary hypertension proved at cardiac catheterization. A reduced diastolic slope of the anterior mitral valve leaflet, simulating mitral stenosis but with normal motion of the posterior leaflet, was observed in all patients. Other features found included a large right ventricular dimension (nine patients), a small left ventricular dimension (three patients), a thick interventricular septum (six patients), systolic mitral leaflet prolapse (four patients) and abnormal septal motion (four patients). The last feature was most probably due to secondary tricuspid or pulmonic insufficiency, or both. The finding of a decreased mitral valve slope, often used as a criterion for mitral stenosis, should not be accepted alone as proof of mitral stenosis; the posterior mitral valve leaflet echo must be carefully searched for and identified. This echo is often difficult to identify, but the normal motion of this structure found in all patients excludes the diagnosis of mitral stenosis as a cause for the pulmonary hypertension.

Primary pulmonary hypertension is an uncommon disease of unknown origin which, in its uncomplicated form, presents the right ventricle with a pure pressure overload.[1] Pulmonary hypertension also is a prominent feature in many patients with mitral stenosis. In rare cases the signs and symptoms may not suggest the correct diagnosis but may completely simulate those of primary pulmonary hypertension.[2,3] Many of these patients with mitral stenosis responded well to surgical treatment.[2] Therefore, treatable mitral valve disease must be definitely excluded when severe, unexplained pulmonary hypertension is encountered.

Since echocardiography provides specific ultrasonic patterns diagnostic of mitral stenosis,[4–7] we examined nine patients with primary pulmonary hypertension documented by hemodynamic studies to determine the relative value of the technique in these patients. Although all nine patients had echocardiographic findings that could be confused with the patterns of mitral stenosis, careful analysis of the records permitted the correct diagnosis. Accordingly, we report these results to emphasize the possible pitfall of making a false positive diagnosis of mitral stenosis in cases of primary pulmonary hypertension, and to present the general echocardiographic features of the right ventricular overload in these patients.

Methods

The nine patients studied had primary pulmonary hypertension documented by historical features, physical examination, electrocardiogram, chest roentgenogram and cardiac catheterization data (Table I). There were three men and six women in the study group, ranging in age from 27 to 54 years (mean age 39 years).

Echocardiographic examinations were performed with a commercially available ultrasonoscope (Smith Kline Instruments, Inc., Palo Alto, Calif.)

From the Cardiology Division, Stanford University School of Medicine, Stanford, Calif. This work was supported in part by National Institutes of Health Grants HL-5709 and HL-5866, and Research Career Development Award 1-K04-HL-704-39 to Dr. Popp. Manuscript accepted June 20, 1973.

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TABLE I

Patient Data

		Echocardiographic Results (mm)								Hemodynamic Results					
										Pressures (mm Hg)					
Case no.	Age (yr) Sex	RV Diast	LV Diast	IVS/LV	MV Slope (mm/sec)	MV Excursion	Post. Leaflet Motion	Syst MV Prolapse	Septal Motion	RV (s/ed)	PAW/LA (mean)	LV (s/ed)	Ao (s/d)	CI	PVR
1	54F	28	40	18/9	48	20(A)	NI	No	NI	72/10	5	113/8	106/68	1.4	14.8
2	44F	32	23	13/8	13	19(A)	NI	Yes	Abn	70/22	7	98/10	97/79	1.4	21.0
3	41M	32	30	16/10	40	17(A)	NI	No	Abn	90/16	16	...	132/84	2.9	7.2
4	32F	22	53	15/8	25	17	NI	Yes	NI	100/17	10	111/12	115/88	1.8	20.1
5	30F	28	40	13/8	57	17(A)	NI	No	NI	91/7	6	160/10	163/74	2.3	13.2
6	30F	32	28	19/10	0	18(A)	NI	Yes	Abn	91/19	9	112/4	101/80	0.8	44.7
7	41F	30	26	17/10	8	16(A)	NI	No	Abn	70/12	6	95/8	97/84	1.5	18.8
8	27M	45	42	15/8	26	16(A)	NI	Yes	NI	102/7	4	...	...	...	...
9	51M	22	51	13/10	28	17	NI	No	NI	116/7	7	127/10	124/77	2.9	10.0

A = contacts septum during diastole; Abn = abnormal; Ao = aorta; CI = cardiac index (ml/min per m²); Diast = diastolic; IVS/LV = interventricular septal thickness/left ventricular posterior wall thickness; LA = left atrium; LV = left ventricle; MV = mitral valve; NI = normal; PAW = pulmonary arterial wedge; Post. = posterior; PVR = pulmonary vascular resistance (units); RV = right ventricle; s/d = systolic/diastolic; s/ed = systolic/end-diastolic; Syst = systolic.

using a 2.25 mHz transducer of 0.5 inch diameter with an acoustic lens providing collimation of the beam for a tissue depth of 5 cm. Patients were studied in the supine position, with the transducer at the left sternal border. Records were made in time-motion presentation while the ultrasound beam was directed along the course of the left ventricular outflow tract, as previously described.[8] Usually no distinct echo could be recorded from the right ventricular endocardial surface, so this surface was estimated to be located 0.5 cm posterior to the chest wall echoes.[9] Echoes were recorded from the right and left sides of the interventricular septum, the anterior and posterior mitral valve leaflets and the endocardial and epi(peri)cardial surface of the left ventricular posterior wall. In some cases the tricuspid valve could be recorded by slight medial, ventral and caudal direction of the sound beam from the position required to record the mitral valve. On these records, measurements were made at end-diastole of right and left ventricular dimensions and thickness of both the interventricular septum and left ventricular posterior wall (Fig. 1). The opening excursion and initial diastolic slope of the anterior mitral valve leaflet were measured, and the motion pattern of the posterior mitral valve leaflet was assessed. In addition, the motion pattern of the echoes from the left side of the interventricular septum and the mitral valve during systole were analyzed. All measurements were correlated and compared with normal values for our laboratory (Table I).

Results

Cardiac Catheterization

Hemodynamic data (Table I) showed that all nine patients had severe pulmonary hypertension. Eight of the nine patients had normal values for pulmonary

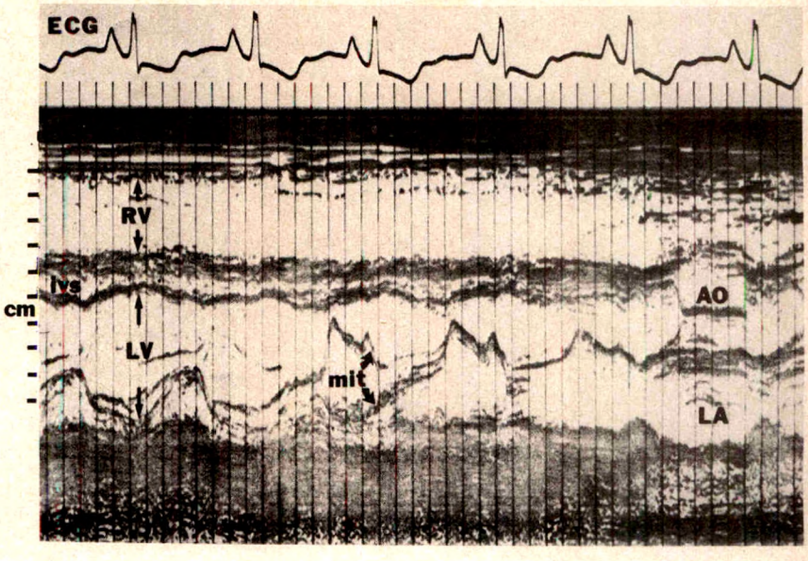

FIGURE 1. Echocardiogram showing a sweep from the aorta **(right)** to the body of the left ventricle **(left).** Measurements of the diastolic size of the right and left ventricles are taken as illustrated. The anterior leaflet of the mitral valve does not contact the septum in diastole, but the early diastolic slope is still reduced below the usually accepted normal range. AO = aorta; cm = 1 centimeter calibration; ECG = electrocardiogram; ivs = interventricular septum; LA = left atrium; LV = left ventricular diastolic dimension; mit = anterior and posterior leaflets of the mitral valve; RV = right ventricular diastolic dimension.

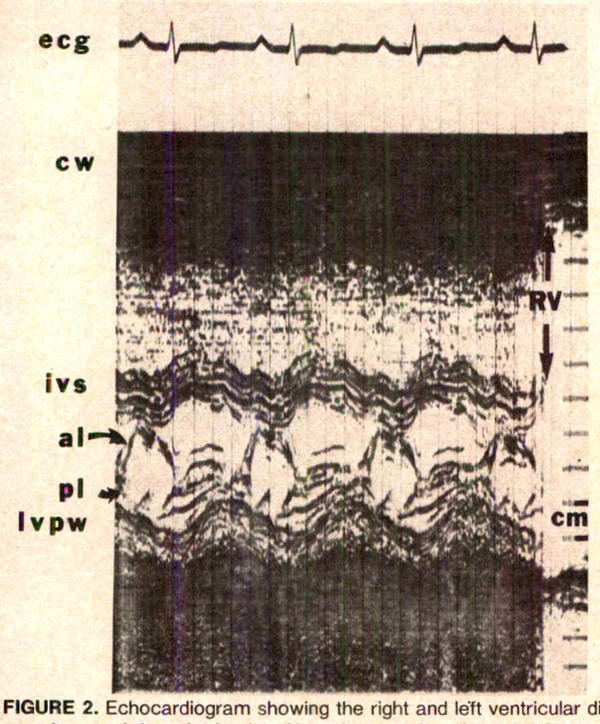

FIGURE 2. Echocardiogram showing the right and left ventricular dimensions and the mitral valve. Note the grossly enlarged right ventricular end-diastolic dimension, best defined by altering the amplification of the signals **(right).** Septal motion is abnormal, since there is no net posterior motion of the left side of the interventricular septum from end-diastole to end-systole. The anterior leaflet of the mitral valve contacts the septum during diastole, with a resulting low slope. Posterior leaflet motion is normal. al = anterior leaflet of the mitral valve; cm = centimeter calibration marks; cw = chest wall; ecg = electrocardiogram; ivs = interventricular septum; lvpw = left ventricular posterior wall; pl = posterior leaflet of the mitral valve; RV = right ventricular end-diastolic dimension.

arterial wedge pressure or left ventricular end-diastolic pressure, or both. In the ninth patient, the mean pulmonary arterial wedge pressure was increased to 16 mm Hg and cardiac index was normal. This level of pressure was out of proportion to the level of pulmonary hypertension found, and the latter was thought to be primary in nature. Oximetry and hydrogen inhalation with a pulmonary arterial electrode failed to demonstrate an intracardiac shunt in any of these patients.

The pulmonary vascular resistance was uniformly increased and cardiac index reduced in six of the eight patients whose data were available. Pulmonary vascular resistance was not affected by the breathing of 100 percent oxygen by mask for 20 minutes.

Echocardiography

All patients had an increased right ventricular dimension, with a range of 22 to 45 mm (mean 30; normal <22 mm) (Table I, Fig. 2). The left ventricular dimension ranged from 23 to 53 mm (mean 37; normal range 30 to 53 mm). One patient had a left ventricular dimension at the lower limit of our normal adult range; three patients had a value clearly below this limit. The interventricular septum was thickened and ranged from 15 to 19 mm in six of these nine patients (Fig. 3) and was at the upper limit of normal in the other three (normal 5 to 13 mm).

The opening excursion of the anterior leaflet of the mitral valve was reduced below normal (>20 mm) in eight of these nine patients, and in seven patients the leaflet appeared to contact the interventricular septum (Fig. 2 and 4). In the two cases in which this contact was not observed, the left ventricular dimension was greater than 50 mm. The initial diastolic slope of the anterior mitral valve leaflet was abnormal in all patients, with a range of 0 to 57 mm/sec (mean 27; normal >80 mm/sec). The anterior mitral valve leaflet maintained contact with the interventricular septal echoes during diastole with apparent interference with valve motion so that both valve excursion and slope were reduced. However, in all patients the motion of the posterior mitral valve leaflet was normal (Fig. 2 and 4).

The systolic motion of the mitral valve was abnormal in four patients. During systole the leaflets moved posteriorly (away from the transducer) instead of showing the normal gradual anterior motion (Fig. 4). This pattern is typical of cases with documented mitral valve prolapse.[10–12] Left ventricular angiograms were performed in Patients 1, 6 and 7 at the time of catheterization. Both the echocardiogram and the ventriculogram of Patient 6 showed mitral valve prolapse; neither technique demonstrated prolapse in Cases 1 and 7.

The echocardiograms of four patients manifested abnormal systolic septal motion with a pattern designated type B by Diamond et al.[13] Instead of the normal posterior motion of the left side of the interventricular septum during systole, there was no net motion from end-diastole to end-systole (Fig. 2).

Discussion

Many of the echocardiographic features described in these patients with primary pulmonary hypertension are those expected with pressure overload of the right ventricle. Thus, the right ventricular diastolic dimension was enlarged. Diamond et al.[13] performed echocardiography in eight patients with pulmonic stenosis and six patients with right ventricular pressure overload from other causes. Two of the patients with pulmonic stenosis and all six of the other patients had an increased right ventricular dimension index (right ventricular dimension/body surface area); the patients with right ventricular failure in addition to the pressure overload had the highest indexes. Six of our eight patients studied by catheterization had right ventricular failure as manifested by increased right ventricular end-diastolic pressure in the presence of a low cardiac index (Table I).

Septal hypertrophy: Right ventricular hypertrophy was evidenced by the thickened interventricular septum found in six patients; in the remaining three patients septal thickness was at the upper limit of normal. No patient had a known cause for left ven-

tricular hypertrophy. The left ventricular posterior wall thickness was within normal limits in all patients. It has been suggested that the ratio of interventricular septal thickness to left ventricular posterior wall thickness be used as a measure of asymmetrical septal hypertrophy and thus as a criterion for the diagnosis of hypertrophic cardiomyopathy.[14,15] Abbassi et al.[14] studied eight patients with nonobstructive cardiomyopathy and described six echocardiographic features of the disease, including a greatly thickened interventricular septum, a normal or only slightly increased left ventricular posterior wall thickness, and a ratio of thickness of the interventricular septum to that of the left ventricular posterior wall of 2.0 or greater. Henry et al.[15] reported asymmetric septal hypertrophy in 15 patients with idiopathic hypertrophic subaortic stenosis, such that the ratio of thickness of the interventricular septum to that of the left ventricular posterior wall averaged 1.68 and was greater than 1.3 in all patients. In all of our nine patients, this ratio was 1.3 or more. This asymmetric hypertrophy of the septum is commonly found in patients with right ventricular hypertrophy.[16]

The left ventricular end-diastolic dimension was abnormally small in three patients and low normal in a fourth. The explanation for this may be related in part to the reduced cardiac output and stroke volume found in these patients. In addition, the shape and position of the left ventricle may be altered by the hypertrophied and dilated right ventricle. In this situation, the left ventricular dimension recorded by ultrasound may not be identical to that recorded in a normal patient. In addition, this dimension could be recorded normally, while reflecting a normal volume distributed within a distorted ventricle.

Abnormal septal motion: Abnormal systolic septal motion, that is, flat or anterior motion of the left side of the interventricular septum during systole, instead of the normal posterior displacement, has been shown to be characteristic of diastolic volume overloading of the right ventricle.[9,13] Secondary tricuspid or pulmonic insufficiency, or both, appeared to be the cause of this abnormal septal motion in the four patients with this pattern. It has been demonstrated that septal motion is normal in patients with a pure right ventricular systolic pressure load.[13]

Mitral valve prolapse: The systolic motion of the mitral valve was abnormal in four patients, demonstrating valve prolapse (Fig. 4). Instead of the leaflets meeting at the beginning of systole and then gradually moving anteriorly, they move posteriorly toward the left atrium.[10–12] Prolapse could be confirmed in the one patient who underwent ventricular angiography. Prolapse has been demonstrated echocardiographically in patients with the mid-systolic click, late systolic murmur syndrome,[10–12] but no patient in our group had findings characteristic of this disorder. It has been postulated that some patients with primary pulmonary hypertension have a connective tissue disorder.[17–21] It then might be expected that mi-

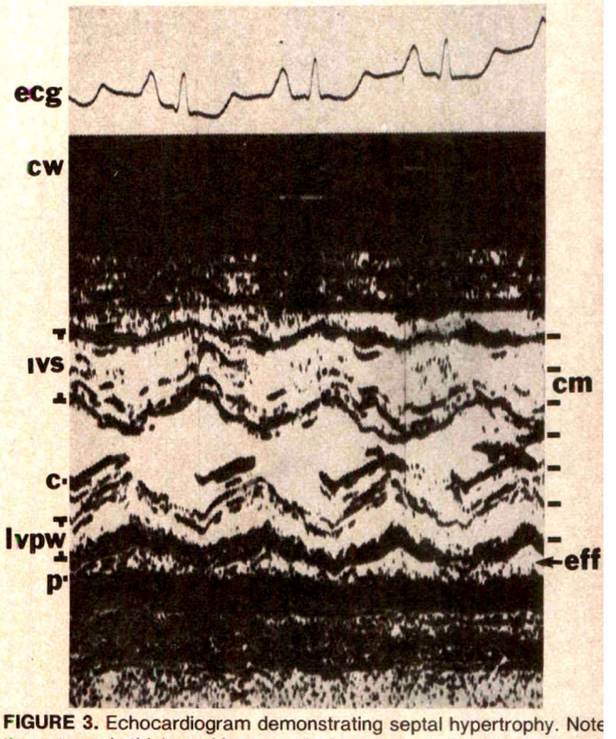

FIGURE 3. Echocardiogram demonstrating septal hypertrophy. Note the extremely thickened interventricular septum with normal left ventricular posterior wall thickness (lvpw). This thickness is well seen because of a small pericardial effusion that defines the epicardium. c = chordae tendineae of mitral valve; eff = pericardial effusion; p = pericardium. Other abbreviations as in Figure 2.

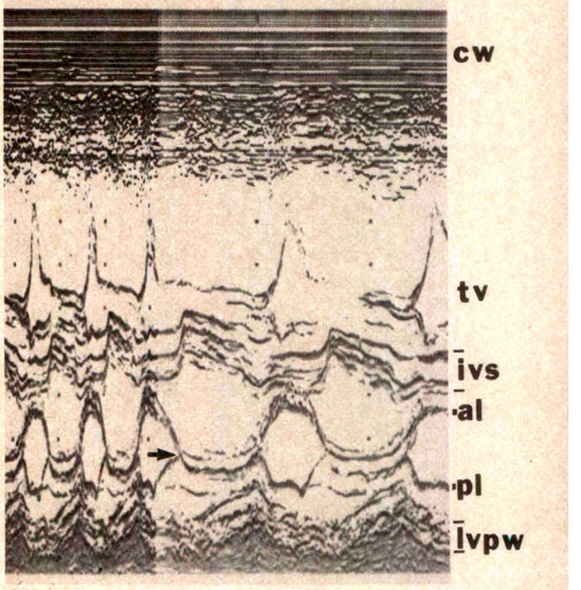

FIGURE 4. Demonstration of mitral valve prolapse. The horizontal arrow denotes the point (C point) at beginning systole when the mitral leaflets apparently meet. The leaflets then move further posteriorly (away from the chest wall) and do not show the normal smooth anterior systolic movement. Also note the contact of the anterior mitral leaflet and the septum during diastole with the normal diastolic motion of the posterior leaflet. No electrocardiogram is recorded. The tricuspid valve (tv) is recorded anterior to the interventricular septum. Abbreviations as in Figure 2.

tral valve prolapse could be related to involvement of the leaflets by such a process. There is support for this hypothesis in the recent demonstration[22] that mitral valve prolapse is a frequent feature of connective tissue disorders.

Abnormal anterior mitral leaflet motion: Perhaps the most important echocardiographic feature in this group of patients concerns the mitral valve pattern during diastole. In every case, the rate of early diastolic motion of the anterior leaflet was reduced, often to a striking degree. Such a reduced early diastolic slope has been used as the hallmark in the diagnosis and the estimation of severity of mitral stenosis.[4–7] In addition, the excursion of the anterior leaflet during diastole was reduced in eight of these nine patients. This finding also is common in rheumatic mitral stenosis.[4–7] Obviously, these patterns might lead one astray in labeling pulmonary hypertension as primary or secondary to mitral stenosis.

In seven of our nine patients, the anterior leaflet contacted the septum, and often maintained contact with the interventricular septum during the entire initial period of left ventricular filling (Fig. 2 and 4). This apparent contact was absent in the two patients with a left ventricular dimension greater than 5 cm. The phenomenon probably results from an abnormally small left ventricular chamber, so that the anterior mitral leaflet abuts on the interventricular septum during early diastole. For this reason, the measured slope probably does not carry the usual connotation related to the rate of left ventricular filling.[23] Duchak et al.[24] showed an echocardiogram of a patient with pulmonary hypertension secondary to venous occlusive disease whose anterior mitral valve contacted the septum and had a very low slope, quite similar to that of our patients. In our two patients whose anterior leaflet did not appear to contact the septum, the diastolic slope was nevertheless reduced (Fig. 1). This finding may be related to a decreased rate of left ventricular filling. Decreased diastolic mitral valve slopes are also found in patients with left ventricular hypertrophy—for example, idiopathic hypertrophic subaortic stenosis[25] and valvular aortic stenosis[23]—and the septal hypertrophy in our patients may lead to the same effect.

Posterior mitral leaflet motion and differentiation from mitral stenosis: Although the slope of the anterior mitral valve leaflet was decreased in all patients, the motion of the posterior leaflet was normal in every case. The recording of the posterior leaflet is of great value in making the diagnosis of mitral stenosis in patients whose anterior leaflet has a low slope.[24] Normally the posterior leaflet is almost a mirror image of the anterior leaflet, opening posteriorly as the larger leaflet moves anteriorly. In rheumatic mitral stenosis, the posterior leaflet moves in the same direction as the anterior leaflet,[24] presumably because of commissural fusion and the larger surface area and mobility of the anterior leaflet. In some of our cases, the echocardiogram from the posterior leaflet was difficult to identify. The excursion of the leaflet was very slight, and great care had to be taken during the echocardiographic examination to record and then to recognize this structure. In this regard, recording the echocardiogram on a strip chart recorder while directing the sound beam back and forth across the area of the junction of the left atrium and left ventricle proved to be the easiest and most reliable method of recording echoes from the posterior leaflet. Without the posterior leaflet as a guide, the mistaken diagnosis of mitral stenosis would have been possible in most of our cases of primary pulmonary hypertension.

It is to be emphasized that in rare instances, patients with mitral stenosis may have signs and symptoms almost indistinguishable from those of primary pulmonary hypertension.[2,3,26] Because surgery can benefit many of these patients, mitral stenosis must be definitively excluded in cases of severe, unexplained pulmonary hypertension.[26] Cardiac catheterization and angiography, which subject patients with primary pulmonary hypertension to a high risk,[26] have been utilized in some cases. Echocardiography may help in the differentiation of these two entities, but only if the pitfalls outlined are avoided.

The correct diagnosis of primary pulmonary hypertension, the degree of right ventricular enlargement and hypertrophy, and the presence or absence of tricuspid and pulmonic valvular regurgitation may be assessed using echocardiography. The echocardiographic picture of primary pulmonary hypertension with secondary tricuspid or pulmonic regurgitation may be difficult to differentiate from that of primary atrial septal defect with secondary pulmonary hypertension. This differentiation requires cardiac catheterization.

Acknowledgment

We thank Nolan R. Corden, MD, Harold M. Lowe, MD, and William Nelson, MD, Col MC for data on their patients, and Mrs. Dorothy McCain and Mrs. Gretchen Houd for preparation of the manuscript.

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Noninvasive Methods for Recording Bundle of His Activity

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The electrode catheter technique for recording electrical activity from various parts of the atrioventricular (A–V) conducting system (particularly bundle of His activity) has significantly contributed to understanding of a variety of A–V conduction and rhythm disturbances occurring within the human heart. Understanding of these events is further enhanced when electrode catheter recordings are made in conjunction with atrial and ventricular pacing procedures. The information derived from the many reported His bundle studies performed in several laboratories has clearly demonstrated both the value and limitations of standard 12 lead electrocardiographic recordings in reflecting underlying electrophysiologic events. It is obvious that not all patients who manifest either a transient or fixed alteration in A–V conduction or rhythm require intracardiac recordings from the specialized A–V conduction system. However, in some patients, bundle of His recordings are indispensable for proper diagnosis and treatment. At present, His bundle electrography is primarily a clinical research procedure although it is relatively simple and safe to perform. The obvious disadvantages of the procedure as currently performed relate to: (1) its invasive nature and the consequent possibility of complications, however minimal; (2) the requirement for catheterization laboratory facilities and equipment, including fluoroscope, multichannel recorder, standby defibrillator; (3) the need to have in attendance two or more physicians and a clinical nurse; and (4) the constant need for awareness of potential electrical hazards.

Perhaps the greatest limitation of the electrode catheter technique relates to the inability to perform repeated sequential studies. Thus, the development of a reliable noninvasive method for recording electrical activity of the specialized conducting system of the heart from the surface of the chest would be a welcome event. The report by Flowers and associates,[1] appearing in this issue of the Journal, represents an initial attempt toward the realization of this goal. These investigators succeeded in recording, from the surface of the chest wall of dogs, activity within the P–R segment of the surface electrocardiogram which they have cautiously termed "blips" and which appear to bear a temporal relation to intracardiac recordings of bundle of His activity. It is obvious that the individual surface recorded "blips" need to be better defined in terms of onset, duration and amplitude. The indefiniteness of some of the "blips" can best be appreciated when the surface recordings are viewed independently of the intracardiac electrograms. Undoubtedly the quality of the surface recordings will improve as technical advances or modifications in the recording apparatus are developed. Additional validation procedures also need to be applied to define more precisely the origin of the successive "blips" as well as the less conspicuous, low amplitude undulations that are also occurring within the P–R segment.

It is important to know whether the surface recorded "blips" represent electrical activity of the right side of the heart exclusively, or whether left-sided activity is also included in these recordings. If the latter is true, then consideration must be given to the effects of cancellation and summation on the configurations and timing of surface recordings. Experiments in which multiple internal recordings of various parts of the His-Purkinje system are made in conjunction with surface recordings under different conditions of A–V conduction and A–V block would substantially assist in the interpretation of the several blips recorded within the P–R segment.

Flowers et al.[1] ascribe the successive "blips" (B_1–B_2) to electrical activity generated within the bundle of His and bundle branch. Their interpretation seems reasonable within the context of their experiments. However, such an interpretation may not be valid under the conditions of an intra-His bundle conduction delay or block which could result in two or more separate His bundle deflections. Furthermore, if the surface recording technique permits simultaneous recordings of His bundle and bundle branch activity then it becomes imperative to define precisely the order in which these deflections occur during ectopic beats. It is also important to determine that the sensing electrodes on the chest wall are recording total His bundle activity. The recordings of A–V nodal activity by electrode catheter and plunge wire technique is a controversial issue. Whether chest wall recordings at high amplification can pick up A–

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V nodal activity presents a challenging problem. In some of the tracings presented, minor base-line undulations precede the His bundle "blip." It needs to be determined whether these undulations represent artifact or A–V nodal or atrial activity.

It is anticipated that all of these questions will be answered as additional experiments are designed and greater experience with the surface recording technique is obtained. Whether this technique will present special problems when it is applied to clinical studies has yet to be determined.

Perfection of the surface recording technique would add a new dimension to the study of electrophysiology in the human heart not only because it would overcome some of the disadvantages cited, but also—and more importantly—because it would permit repeated studies in the same patient.

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Preinfarction Ill Health

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Death from myocardial infarction frequently occurs before medical help can be obtained. This is a tragedy because the prognosis of the resuscitated patient is as good as that of the patient who does not require resuscitation.[1,2] Many lives might be saved if the approaching infarction could be recognized early enough for preventive action to be taken. Unfortunately, angina pectoris and electrocardiographic changes, the traditionally accepted warning signs, have failed to predict oncoming infarction and sudden death.[3] It may prove more profitable to seek other warning symptoms and signs.

Preinfarction Symptoms

Over the past few years, the importance of fatigue as a precoronary symptom has begun to be recognized. Kinlen[4] interviewed the relatives of 142 victims of apparently sudden and unexpected death from coronary artery disease and found a history of tiredness and loss of energy in 41 percent:

"It was striking how often a certain pattern of changed behaviour was described in these cases of sudden death. A man who normally did a good deal of work in the garden might give this up. He might complain of tiredness or of 'getting old,' but more often it was the case that his wife would notice him going to bed earlier in the evening or falling asleep in chairs where this was previously very unusual. In 2 cases the patient even fell asleep during meals .... The duration of these symptoms varied from two weeks to six months."

Relatives were also aware of a recent change in appearance, unusual coldness of the limbs and irritability in the weeks before death. When Kinlen interviewed surviving patients with myocardial infarction he found that these symptoms were rarely volunteered.

Tiredness and reduced activities: In an attempt to clarify the symptoms experienced before infarction, we recently questioned 40 consecutive survivors of acute infarction and, wherever possible, a close relative (Table I). The majority of the patients had a history of declining health over many months before the infarction, and two separate groups of symptoms could be recognized. One group of symptoms included tiredness and reduction of activity. Thirty-one of the 40 patients (77 percent) had suffered from an increasing and abnormal fatigue for 6 weeks to 3 years before the infarction. Excessive sleeping at inappropriate times had been noticed in 32, and in 29 (72 percent) of these this symptom was new or had increased. Typically, for 1 or 2 years before the infarction the patient had habitually fallen asleep in a chair during the evening while watching television, and sometimes on other occasions. In 32 cases (80 percent) a history of general "slowing down" and accelerated aging was obtained from the patient or relative, or both. Altered patterns of behavior were common. Libido had begun to decline in nine (22 percent). Irritability was more marked in 25 (67 percent), and the relative was usually more aware of this change than the patient. A reduction in social and leisure activities had been noticed in 25 cases (67 percent). Often the patient had stopped going out in the evening or had eliminated activities involving physical exertion such as playing golf, gardening or performing "do-it-yourself" tasks about the house. These symptoms of fatigue and diminishing energy and stamina are similar to the symptoms that often precede the onset of frank dyspnea in mitral incompetence.[5,6] In coronary artery disease these same symptoms may also be attributed to left heart dysfunction impairing the ability of the heart to increase its output in response to emotional and physical challenges.[7]

Limited exercise tolerance: The other group of symptoms comprised those that limited exercise tolerance. Angina pectoris occurred late in the period of declining health and in only half the patients. A further 10 (25 percent) had had their exercise tolerance progressively reduced by dyspnea. In eight of these the dyspnea was recognized as different from normal, not only in that it came earlier, but also in that it imposed an absolute barrier to further exertion and had an unpleasant quality variously described as "uncomfortable," "constricting," "choking" or "tight." This

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barrier to continued exertion we have called a "standstill factor." The standstill factor and angina pectoris may well have a common origin in the sharp increase in left ventricular diastolic pressure in response to physical or emotional demands which is known to precede most attacks of anginal pain. In coronary artery disease there are many different causes of left ventricular dysfunction. These include long-standing atheromatous narrowing or occlusion of coronary arteries, minor coronary thromboses and platelet emboli, mitral incompetence from papillary muscle ischemia, and the hypertensive, lipidemic, platelet sticking consequences of an aggressive, self-destructive way of life.[8] Left ventricular damage from previously unrecognized infarction is a common finding when death from coronary disease has been sudden and unexpected.[9,10]

Denial of Symptoms

During our study of preinfarction symptoms, it was very noticeable that relatives were much more likely to volunteer information and be emphatic about changes in health than the patients themselves. The patient characteristically tended to minimize or conceal disability and to rationalize symptoms or attribute them to the inevitable consequences of aging. This tendency to deny or minimize disability that has become obvious to others might account for the differences between the histories Kinlen obtained from the survivors of acute infarction and the histories he obtained from the relatives of those who died.[4] This tendency may also contribute to delayed hospital admission after myocardial infarction,[11,12] and may be one reason why up to 30 percent of the infarctions revealed by population studies had not been recognized clinically.[13–15] The denial of disability appears to be an exaggeration of the normal mechanism for concealing inadequacy and declining ability as described by Kennedy.[16] This mechanism is likely to be particularly well developed in the patient with coronary disease whose pride and scorn of physical frailty may not allow him to acknowledge illness that threatens his security.[17]

Causes of Breakdown in Health

The environmental challenges that may cause breakdown in the health of industrial managers have also been described by Kennedy.[16] These same factors, with some additions, seem to have been prominent in causing the cardiac breakdown in many of our patients. This is hardly surprising in view of the gross biochemical changes that may be precipitated by everyday stresses[18] and frequent life changes.[19] Challenges in the working environment include transfer to new tasks, failure to achieve, frustrations and defeat imposed by others, actual or threatened loss of employment, loss of a colleague, change of management or management policy, change of place of work (particularly if this involves rehousing or more arduous traveling), oncoming retirement for which one is inadequately prepared and conflict between the demands of the job and the demands of the family.

TABLE I

Prevalence of Preinfarction Symptoms in 40 Consecutive Survivors of Acute Myocardial Infarction

Symptom	Patients Affected (%)
Slowing/aging	80
Abnormal fatigue	77
Excessive sleeping	72
Increased irritability	67
Reduction in leisure activities	67
Angina pectoris	52
Atypical chest pain	37
Increased dyspnea on effort	25
Reduced libido	22
"Standstill factor"	20

Challenges in the home environment include moving to a new house, loss of community ties, bereavement and the strain of bereavement anniversaries, involvement in lawsuits, adultery or divorce, incompatibility in marriage and confrontation with rebellious offspring. These causes of breakdown are likely to be nurtured and aggravated by persons of a restless and aggressive nature who create conflicts and crises by their attitudes and behavior. Friedman and Rosenman and their co-workers[20–22] have described the individual with an aggressive personality, enhanced competitive drive and inability to relax whose blood cholesterol level is raised and whose blood coagulability is increased during stress and who runs an unusually high risk of myocardial infarction. MacKinnon[23] regards the patient with coronary artery disease as self-destructive, and Nixon[24] sees him as addicted to work and tension. Carruthers[8] has indicated how aggression causes excessive catecholamine secretion, high levels of free fatty acids, lipidemia, platelet stickiness and predisposition to thrombus formation and atheroma. These self-injurious consequences of aggression are aggravated by sloth, gluttony and cigarette smoking, which may themselves result from excessive strain and tension.

Implications of the Symptoms

If one accepts as a working hypothesis that coronary illness is largely a self-inflicted breakdown in health consequent on too much strain and tension, and that left ventricular dysfunction may give rise to the changes described here before the occurrence of pain and electrocardiographic changes, a number of implications may modify the traditional clinical approach to coronary illness:

1. Public health: During the past 100 years Western social evolution has presented an ever increasing rate of challenges to adaptation. This situation is recognized to be dangerous psychiatrically,[25] and knowledge of the biochemical consequences of stress suggests that it is also dangerous cardiologically. A

reduction in the morbidity and mortality from coronary heart disease might be achieved by teaching industrial concerns and individuals that overcompetitive and stress-producing habits at work and leisure ultimately promote ill health. However, a substantial decrease in the incidence of coronary heart disease in Western countries seems unlikely to be achieved without a complete restructuring of society and a reduction in the aggressive, competitive and insecurity-generating drives presently encouraged and rewarded by capitalist nations.

2. Early diagnosis: In both England[4] and the United States,[26] it has been found that about a quarter of the victims of sudden death from coronary artery disease had visited a doctor in the week before their death without obtaining protection. Some of these subjects might be identified if doctors were taught to think of coronary illness when they encounter declining physical ability in the overstressed patient, and to seek further evidence of impaired left heart function. Often the earliest sign of left ventricular dysfunction is the palpable and audible atrial gallop.[27] This is most easily detected by turning the patient on his left side where the gallop may be more easily palpated than heard. We regard the presence of the symptoms described here together with clinical evidence of abnormal left ventricular function as a "preinfarction syndrome" warranting urgent treatment. Even if the patient is just overstressed and exhausted, it does no harm to rest him, provided that cardiac neurosis is not produced, and it should be beneficial to manipulate his attitudes and behavior as one would with a patient who had established coronary heart disease.[28]

3. Management of the symptomatic patient: Lack of interest in the early diagnosis of coronary disease is associated with the widely held belief that the course of the disease cannot be altered. This is unfortunate because there is good pathologic evidence that collateral circulation can develop to bypass coronary obstruction,[29–31] and that recanalization of vessels blocked by atheroma or thrombosis can result in a normal lumen.[32] Fulfilling the anatomic and physiologic potential for recovery from coronary artery disease requires that the causative and aggravating factors be modified. Our therapeutic approach to the symptomatic "preinfarction" patient or the subject with angina has been to rest him until he is free from symptoms, and then to set about modifying the attitudes and environmental factors that appear to be contributing to his illness.[33,34] After the patient has rested adequately, there should be such an improvement in his well-being as to convince him that he can climb out of the decline if he continues to discipline his addiction to work and tension and to live in an unstrained fashion. His recovery of physical fitness may be accelerated by a course of training in a gymnasium,[24] with the aim of making exercise a part of his routine of living. He should learn to achieve the peaceful yet active way of life he has denied himself in the past, delegate responsibilities, refuse excessive work loads and enjoy leisure.

4. Rehabilitation after myocardial infarction: A similar approach is required for the patient who has had a myocardial infarction. Before he is discharged from the hospital, his attitudes and environment must be prepared for his recovery and survival, and his progress in understanding his problems and the necessity for changing his life style should be a major factor in determining the length of his stay in the hospital.[35] If the patient believes that his infarction came without warning, invitation or cause, the rehabilitation is extremely difficult because he lives in constant fear of another attack. Failure to return to work after myocardial infarction is as likely to be caused by anxiety or depression as by cardiac disability.[36] A clear understanding of his preinfarction symptoms and the factors that produced them equips the patient and his family to protect his future. He can be taught to recover confidence and increase his physical fitness with an exercise program. He can be taught to work hard without generating tension and to lose his sense of guilt during relaxation. Under these conditions he is more likely to observe recommendations to lose weight or give up smoking. The treatment of elevated blood pressure and serum lipid levels may be obviated by their return to normal levels. The idea of working for recovery rather than passively accepting medical treatment appeals to many patients.

Conclusion

Not every patient with the symptoms described here has coronary heart disease, nor do these symptoms precede every episode of myocardial infarction. But we consider it rational and prudent to consider the diagnosis of coronary disease and to seek evidence of abnormal heart function when a patient presents with abnormal fatigue and other symptoms of declining health. In treating a patient with established coronary artery disease, it is worthwhile to make an initial assumption that he has undergone the decline in health described here and that the extrinsic and intrinsic causes of his breakdown can be manipulated well enough to allow recovery of well-being and physical ability.

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ABSTRACTS: ADDENDUM*

CORRECTIVE CARDIAC SURGERY IN INFANCY: PROFOUND HYPOTHERMIA AND CIRCULATORY ARREST TECHNIQUE

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Correction of congenital heart defects in infancy is desirable and is facilitated by the technique of profound hypothermia and circulatory arrest. Forty-three infants underwent surface cooling and rewarming.

Correctable Lesions:

Lesions	# Patients	Op. Mortality
Ventricular Septal Defect	10	1
Tetralogy of Fallot	12	0
Atrioventricular Canal	4	1*
Transposition of Great Arteries	10	2
Intact Ventricular Septum	6	1
Ventricular Septal Defect	4	1*
DORV (type I)***	1	0
TAPVC****	1	0
	38	4 (10%)
Non-Correctable Lesions:		
DORV (type III)***	1	1
Truncus Arteriosus	2	2**
Cardiac Tumor	1	1
Pulmonary Venous Atresia	1	0
	5	4 (80%)
TOTAL	43	8 (18.5%)

*Prosthetic valve replacement.
**1. Complete atrioventricular canal, 2) Advanced PVO + truncal valve insufficiency (4+).
***Double outlet right ventricle.
****Total anomalous pulmonary venous connection.

Seventeen infants weighed less than 4 kg., the smallest child to survive corrective surgery was an 11 day old (2.2 kg) premature with tetralogy of Fallot. Details of the operative technique and postoperative care will be discussed.

SURGICAL ANATOMY OF OBSTRUCTING MUSCLE BANDS OF THE RIGHT VENTRICLE IN TETRALOGY OF FALLOT

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We have studied 197 (118 unoperated and 79 operated) autopsied hearts with tetralogy of Fallot in order to categorize the various obstructing muscle bundles in the right ventricle and provide a practical and useful descriptive nomenclature. Using the center of the arch or crista supraventricularis as a reference, the obstructive muscle bundles were divided into three groups: septal, when the obstructing bands were maximal on the septal side of the arch; parietal, when on the parietal side; or combined. These were also described as above, at, or below the level of the crista. Of the 118 unoperated hearts there were 12 classified as having primarily the septal type of obstructive bundle, 30 as the parietal type and 65 as the combined type. In 11 hearts we observed the so-called excavated crista pathology where the arch was minimal or non-existent. Fourteen hearts exhibited, additionally, an aberrant muscle bundle that crosses from the septum to the parietal wall. Observations were made on the 79 operated postmortem hearts where some of the obstructive muscle bundles were not adequately identified and resected. This study will guide the surgeon toward a more complete removal of the obstructive pathology.

EFFECT OF MATERNALLY ADMINISTERED DIGOXIN UPON FETAL CARDIAC OUTPUT

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The effect upon the fetal left ventricular output, (LVO), of a chronically digitalized mother is unknown. Placental transfer of tritiated digoxin, (tD), when the drug is chronically administered to the ewe during the entire pregnancy in dosage equivalent to that in man was studied, and the short term preservation of LVO in the exteriorized fetus at the termination of the pregnancy was evaluated. Seven ewes were given 6 μg/kg body weight, (bw), of tD daily (20 per cent of total digitalizing dose 0.03/kg) bw for the entire pregnancy. The fetus was exteriorized between the 120 and 140 days of gestation and the LVO determined serially by dye-dilution technique for one hour. The ewe and its fetus were then killed, and the mean tissue concentrations in μg/gm for the ewes were: heart, 5.7 ± 1.76; liver, 3.38 ± 1.38; kidney, 41.9 ± 12.3. Corresponding values for the fetuses were: 1.55 ± 1.01; 0.78 ± 0.35; 2.48 ± 1.18. The mean serum level for the ewe at end of one hour was 1.65 ng/ml ± 0.48 and for the fetus 1.22 ± 0.20. The amniotic fluid contained 1.45 ng/ml ± 0.27. At the end of one hour the mean LVO had decreased by 39 per cent ± 15 of its control value. This study again confirms that tD crosses the placenta. Although the fetal serum level of tD was similar to that found in the mother and the amniotic fluid contained significant amount of tD, the fetal tissue concentration of tD was not sufficient to produce any demonstrable inotropic effect as measured by the LVO in contrast to acute administration of tD (0.03 mg/kg) bw which did preserve fetal myocardial function but the tissue levels of the fetus in this instance were greater by a factor of 10, (previously reported work from this laboratory).

OCCURRENCE OF ASYMMETRIC SEPTAL HYPERTROPHY (ASH) IN INFANCY.

Barry J. Maron, MD; Jesse E. Edwards, MD; Walter L. Henry, MD; Chester E. Clark, MD; and Stephen E. Epstein, MD, NHLI, Bethesda, Md.

Asymmetric septal hypertrophy (ASH) is a disorder of cardiac muscle characterized by disproportionate hypertrophy of the ventricular septum (ratio of septal to left ventricular free wall thickness >1.3) that appears to be transmitted as an autosomal dominant trait. Disorganization of cardiac muscle cells is a characteristic histologic feature of the disease. ASH has been recognized only rarely in early childhood and has not been documented in the first few months of life. It thus has not been considered among the causes of infant death. However, we have found ASH at necropsy in two male infants, aged 5 mos and 1-1/2 mos, and a male stillborn. The two infants had severe congestive heart failure; a loud systolic ejection murmur in both suggested the presence of outflow obstruction. Septal to posterobasal left ventricular free wall thickness ratios were 2.3 and 2.6 in the infants and 1.9 in the stillborn. Histologic examination of myocardium from the ventricular septum demonstrated morphologic abnormalities similar to those present in adult patients with ASH; muscle cells were markedly hypertrophied and small foci of abnormally oriented muscle cells were present. Numerous disordered bundles of hypertrophied muscle cells were interlaced among more normally arranged cell bundles. These morphologic findings were less marked or absent in the left and right ventricular free walls. Echocardiographic studies documented ASH in asymptomatic relatives of all three infants. These observations provide further evidence that ASH is a genetic disorder and indicate that the disease may be clinically manifest in infancy. Whether this disease is a rare or common cause of cardiac death in infancy is unknown.

*Abstracts from papers presented at the 23rd Annual Scientific Session of the American College of Cardiology, February 11–14, 1974. They should be added to those published in the January issue of the Journal (Am J Cardiol 33:121–180, 1974).

CARDIAC CATHETERIZATION AND SELECTIVE ANGIOGRAPHY IN INFANTS WITH A NEW FLOW-DIRECTED CATHETER.
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The overall risk of serious complication during cardiac catheterization in infants less than 30 days of age is reported to be as high as 15%. Cardiac perforation during catheter manipulation and selective angiography accounts for the majority of deaths in this age group. It is the purpose of this presentation to report the development and use of a prototype flow-directed infant angiography catheter* which minimizes the occurence of these complications. This double lumen 5F 60 cm. cathter combines both the flow directed (gas filled balloon) features of the standard Swan-Ganz catheter with the highflow contrast delivery characteristics of the standard NIH infant angiography catheter. These features provide easy accessibility to all cardiac chambers and great vessels with virtually no risk of perforation and minimal arrhythmia as well as delivery of contrast at high flow rates through side holes proximal to the balloon for selective angiography of diagnostic quality without fear of intramyocardial injection. Preliminary experience with 16 infants demonstrates the value of this catheter in providing a safe and rapid method of R & L heart catheterization and selective angiography.

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EARLY PRIMARY REPAIR OF TETRALOGY OF FALLOT
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Thirty-three children under the age of five years who have undergone corrective surgery for Tetralogy of Fallot in the last four years are presented. In 22 children, (Grp.1) primary correction (no previous shunt procedure) was done with one death. There were no deaths in a group of eight infants under two years of age. Eleven children (Grp.2) underwent secondary correction after one or more shunts and there were two deaths in this group. There was little patient selection in Grp.1. All patients were moderately or severely cyanotic, some with cyanotic spells. In no instance was an acyanotic child operated to prevent "progression of the disease". The only contraindication to primary correction was hypoplasia of the pulmonary artery branches. Hypoplastic conus, severe infundibular stenosis and annular hypoplasia do not preclude primary corrective surgery. The youngest patient who underwent successful primary repair was five weeks old. It was observed in the infant group (<two years) that the major determinant of successful outflow repair was an annulus diameter >than 12 mm. If preliminary inspection and measurement of the annulus revealed a diameter <12mm., an outflow patch of pericardium was used.

Deep hypothermia and circulatory arrest in children 15Kg. in weight greatly facilitated the operative technic. Heart block was not encountered and outflow aneurysm was seen in only one patient who had residual distal obstruction.

It is proposed that primary correction rather than two stage operation should be offered to infants and young children with Tetralogy of Fallot in view of the acceptable mortality and lack of long term morbidity.

Young Investigators Awards Competition Finalists

INTRAMYOCARDIAL PRESSURE: THE EFFECT OF PRELOAD ON THE TRANSMURAL DISTRIBUTION OF SYSTOLIC CORONARY FLOW
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Impairment of systolic coronary blood flow (CBF) may be mediated by intramyocardial pressure (P_{IM}). However, the effect of systole on the magnitude and transmural distribution of CBF has not been investigated. The purpose of this study was to measure this and indirectly P_{IM}. It is assumed that P_{IM} acts on the coronary vessels as a Starling resistor, such that local CBF is determined by the equation: $P_c - P_{IM} = R \cdot CBF$, where P_c is coronary perfusion pressure and R resistance. This equation was integrated with respect to time and solved simultaneously for P_{IM} and R by measuring regional CBF (radioactive microspheres) during maximal coronary vasodilitation in two states: beating and hypocalcemic diastolic arrest. Measurements were made in 7 to 16 concentric layers of the left ventricle (LV) of 16 dogs. P_{IM} ranged from near zero to twice peak LV pressure. The transmural distribution of P_{IM} and systolic CBF depended on preload. The transmural distribution of the ratio of P_{IM} to P_c was not significantly different from one across the LV wall at low preload (0-4mmHg). At moderate to high preload (7-35mmHg) in the inner two 1/5 of the LV wall this ratio was not different from unity (mean 1.03 and 0.96), but in the middle and two outer 1/5 this was significantly lower(mean 0.79, 0.64, 0.41 respectively). These data show that P_{IM} shuts off systolic CBF across the entire LV wall at low preload and at high preload P_{IM} determines a gradient of decreasing systolic CBF from the subepicardium to zero in the subendocardial layers. This suggests that dilated or failing LV receive systolic flow to the outer myocardial layers, where as, at low preload myocardial perfusion is entirely diastolic.

REGIONAL WALL MOTION ABNORMALITIES OF ACUTE MYOCARDIAL ISCHEMIA: EFFECTS OF CORONARY REPERFUSION WITH AND WITHOUT ALTERATIONS OF ARTERIAL PRESSURE AND HEART RATE.
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The effect of alterations in blood pressure (BP) and heart rate (HR) on segmental dyskinesis induced by acute coronary ligation, and on the subsequent response to coronary reperfusion (CR) was evaluated in 77 open-chest dogs. Wall motion was recorded by ultrasound reflected directly off the ischemic muscle. Acute ischemia (I) produced characteristic regional wall motion abnormalities: aneurysmal bulging during isometric contraction and markedly reduced wall velocity (WV) during ventricular ejection. During 60 minutes of I the dogs underwent interventions to raise BP 25-50%: methoxamine (M), phenylephrine (P) or norepinephrine (NE); other animals had BP lowered 25-50% with nitroprusside (NP) or hemorrhage (H) during I, or underwent atrial pacing (AP) to increase HR 25-50%. A control group (C) underwent no intervention during I. During I WV was markedly reduced by M and improved by NE. After cessation of drugs and 60 minutes of CR the relative order of improvement of WV was: NE: 11+2 mm/sec (ischemia) to 24+3 mm/sec (reperfusion), C: 12+3 to 20+3, NP: 13+2 to 20+1, H: 10+2 to 18+2, AP: 14+1 to 20+2, PE: 9+1 to 9+2, M: 14+2 to 12+1. The aneurysmal bulging during isometric contraction also was reduced to a greater degree after NE than other interventions. The deleterious effects of increased afterload with M or PE thus outweighed the beneficial effects (increased coronary perfusion) and exacerbated the dyskinesis of the central portion of the ischemic area during the drug and after CR. NE, however, reduced dyskinesis, probably by decreasing ventricular size and wall tension. We conclude that elevation of BP, although known to reduce infarct size, may have deleterious effects on regional wall motion abnormalities depending on the pressor agent used.

THE RELATIONSHIP BETWEEN CORONARY PERFUSION PRESSURE, FLOW, AND RESISTANCE IN STENOSED HUMAN CORONARY ARTERIES: THE CRITICAL IMPORTANCE OF SMALL CHANGES IN % STENOSIS.

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Nineteen proximal coronary arteries with varying focal stenoses (2%-98%) were dissected from fresh post mortem adult hearts and perfused with isotonic glycerol saline (n=2.7 centipoise) at constant pressures of 30, 50, 75, 100, 150 and 200 mmHg, while varying the distal bed resistance (r_b) over the range 0.1 to 5 mmHg/ml/min. Flow rate (Q) and arterial segment pressure drop (ΔP) were measured at each perfusion pressure and r_b, and a permanent cast of silicone rubber was made under 100 mmHg pressure following perfusion. Hydraulic resistance ($R=\Delta P/Q$) was proportional to a Poiseuillian scaling ($R_o \alpha 1/r^4$) at lowest flow rates (10-30 ml/min), with R increasing to 2 or 3 times R_o at higher flow rates (30-100+ ml/min). Curves of flow rates vs. % stenosis showed that flow rate was relatively constant with stenoses less than 70-80%. With a small further increase in stenosis, however, flow rate decreased dramatically. Furthermore, significant reductions in flow rate occurred at lower % stenoses for greater demands (lower r_b). Elastic effects were important in arteries with an eccentric lesion, in that an 80% eccentric stenosis had an additional flow loss of 5% (as compared to a concentric stenosis) when the perfusion pressure was lowered from 100 to 70 mmHg. In conclusion, small changes in % stenosis, perfusing pressure, or increased "demand" (decreased r_b) had dramatic effects on the pressure-flow relationship across focal lesions in human coronary arteries. These results have important implications relative to the quantitation of lesions on coronary angiograms, the alteration of perfusing pressure or changes in myocardial O_2 demand.

CAPILLARY AND CELL WALL PERMEABILITY TO POTASSIUM IN ISOLATED DOG HEARTS

Robert G. Tancredi, MD; Tada Yipintsoi, MD; James B. Bassingthwaighte, MD, Mayo Clinic, Rochester, MN.

From venous tracer-dilution curves recorded after 34 pulse injections of ^{42}KCl and ^{131}I-labeled albumin into the coronary artery inflow of six isolated canine heart preparations, we calculated maximal fractional extractions (E_{max}) and capillary permeability-surface area products (PS_{cap}) for K^+ over a range of plasma flows (F_p) from 0.4 to 1.6 ml min^{-1} g^{-1}. At low F_p (< 1.0), E_{max} was 0.56 ± 0.05 (mean ± SD) and PS_{cap} was 0.59 ± 0.18 ml min^{-1} g^{-1}; at high F_p (>1.0), E_{max} decreased to 0.47 ± 0.08 and PS_{cap} increased to 0.84 ± 0.22. Continuous recording (gamma detector) of residual $^{42}K^+$ in four additional hearts showed that the fractional escape rate of tracer became constant at 0.008 to 0.010 min^{-1} at 2 to 4 hours after injection. The cell wall and the capillary membrane are the primary barriers to $^{42}K^+$ washout from the sarcoplasm. Using PS_{cap} measured at various flows and considering the virtual intracellular volume of distribution for K^+ to be 20 ml/g, we calculated the permeability-surface area product for sarcolemma, PS_{cw}, as 0.18 to 0.29 ml min^{-1} g^{-1}. On the basis of sarcolemmal surface area (S_{cw}) of 4,200 cm^2 g^{-1} and capillary surface area (S_{cap}) of 500 cm^2 g^{-1}, cell permeability is very low, with $P_{cw}:P_{cap}$ being 0.02 to 0.06. We concluded that the cell membrane provides the major resistance to the exchange of K^+ between sarcoplasm and capillary blood.

INVESTIGATION OF THE MECHANISM OF THE INOTROPIC EFFECT OF HYPERTONIC MANNITOL IN ISOLATED CARDIAC MUSCLE AND OF MANNITOL'S INFLUENCE ON REGIONAL MYOCARDIAL BLOOD FLOW IN DOGS WITH MYOCARDIAL ISCHEMIA

James T. Willerson, MD, U. Tex. Southwestern Med. Sch. at Dallas, Dallas, Texas.

To further evaluate the potential ability of hypertonic mannitol (M) to improve myocardial performance and increase coronary blood flow the following studies were performed. Forty-five isolated isometrically-contracting cat papillary muscles were studied in Krebs-Ringers bicarbonate with 18 mM glucose and varying extracellular calcium concentrations. Six awake unsedated and 21 anesthetized dogs on right heart bypass (RHBP) with acute myocardial ischemia (AMI) were also evaluated. M (50 mOsm above control) significantly increased developed tension (DT) and the maximal rate of tension rise (dT/dt) in isolated cardiac muscle in 2.5 mM Ca but significantly depressed DT and dT/dt in 10 mM calcium. Norepinephrine (10^{-6} M), however, significantly increased DT and dT/dt in 10 mM Ca in the same muscles. D600 (10^{-6} M), a potent pharmacological inhibitor at the cell membrane of the intracellular transfer of calcium, decreased DT and dT/dt by 75% and completely abolished the inotropic effect of increasing stimulation rate (treppe) but did not alter M's inotropic effect. Paired pacing produced the same changes as M. Myocardial ischemia (AMI) was produced by 10 minutes of proximal LAD occlusion. Regional myocardial blood flow (RMBF) was measured using radioactive microspheres (8μ). In awake dogs M (20 mOsm above control) significantly improved ventricular performance and increased RMBF 30-50% to all myocardial areas. In anesthetized dogs on RHBP M significantly increased RMBF to the RV, the ventricular septum, the nonischemic LV, and the total LV by 30-40%. RMBF to the LV ischemic area significantly increased by 15%. The increases in RMBF in dogs on RHBP after M occurred without significant changes in cardiac output, heart rate, and mean arterial pressure. In awake, unsedated dogs with AMI M produced essentially the same increases in RMBF. These data suggest that the inotropic effect of M in isolated cardiac muscle is critically dependent on and linked to alterations in intracellular Ca and not significantly influenced by inhibition of cell membrane systolic Ca flux. M *in vivo* increases RMBF to all myocardial areas in awake and anesthetized dogs with AMI suggesting its potential ability to limit the area of AMI under physiological circumstances.

BOOK REVIEWS

MYOCARDIAL BLOOD FLOW IN MAN, METHODS AND SIGNIFICANCE IN CORONARY DISEASE, edited by A. Maseri. Torino, Minerva Medica, 1971, 576 pages

This volume consists of the proceedings of an international symposium drawing together recognized experts to discuss methods in research into myocardial blood flow. Published under the auspices of the World Health Organization, it represents the latest sum of knowledge and opinions up to June 10, 1971—the time the conference was held. It is an excellent reference for advanced students of the subject who plan to utilize these methods in clinical studies. It is not recommended for the general practicing physician, medical student or even the cardiologist who is not one of the limited group of experts familiar with the methodology, mathematics and language of this important aspect of cardiologic research. Since there is no systematic attempt to begin from the beginning, the papers are, by and large, intelligible only to those who already have considerable basic knowledge and experience within the field.

A major section is devoted to theoretical and technical problems in myocardial blood flow measurement in man. There is an excellent paper by K. L. Zierler in this section concerning the mathematical analysis of assumptions and limitations of the measurements of absolute flow, outflow detection, relative blood flow by residue detection and external monitoring by cinedensitometry. The application of these methods to evaluation of the patient with coronary disease is also treated in papers on use of the nitrous oxide method, xenon clearance, thermistor method of detection of coronary sinus outflow, among others. Methods of studying and quantifying blood flow inhomogenity within the myocardial wall are presented, and the singular significance of this aspect of coronary blood flow is emphasized. Overperfusion of relatively normal myocardial vascular beds can conceal the presence of underperfusion of diseased areas when total flow alone is measured. Finally, there is a roundtable on the clinical correlation of ischemic heart disease, and the present methods of study and guidelines for future research are summarized by Dr. L. Donato after an extensive discussion by Drs. G. Baroldi, R. J. Bing, R. Gorlin, D. E. Gregg, M. McGregor, M. F. Oliver, A. Schwartz, E. H. Sonnenblick, E. Varnauskas and K. L. Zierler.

Richard P. Lasser, MD
New York, N. Y.

REVIEWS IN CARDIOLOGY*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ANGINA PECTORIS

Editorial: Nitrates in the prophylactic treatment of angina pectoris. Goldstein RE, et al. **Circulation 48:917-20, Nov 73 (17 ref.)**

Angina pectoris: diagnosis, evaluation and therapy. Tempero KF. **Geriatrics 28:76-81, Nov 73 (17 ref.)**

ANTIHYPERTENSIVE AGENTS

The mechanisms of action of some antihypertensive drugs. Laverty R. **Br Med Bull 29:152-7, May 73 (97 ref.)**

Hypertension, antihypertensive drugs and atherosclerosis. Hollander W. **Circulation 48:1112-27, Nov 73 (118 ref.)**

ARTERIOSCLEROSIS

Hypertension, antihypertensive drugs and atherosclerosis. Hollander W. **Circulation 48:1112-27, Nov 73 (118 ref.)**

BLOOD VESSELS

The actions of drugs on the smooth muscle of the capsule and blood vessels of the spleen. Davies BN, et al. **Pharmacol Rev 25:373-413, Sep 73 (262 ref.)**

CEREBRAL ARTERIOSCLEROSIS

Hypertension, antihypertensive drugs and atherosclerosis. Hollander W. **Circulation 48:1112-27, Nov 73 (118 ref.)**

CEREBROVASCULAR DISORDERS

Report of the joint committee for stroke facilities. IX. Strokes in children. 1. Diagnosis and medical treatment of strokes in children. **Stroke 4:871-94, Sep-Oct 73 (92 ref.)**

CORONARY DISEASE

Hypertension, antihypertensive drugs and atherosclerosis. Hollander W. **Circulation 48:1112-27, Nov 73 (118 ref.)**

HEART

The molecular and ionic basis of altered myocardial contractility. Kones KJ. **Res Commun Chem Pathol Pharmacol 5:1-84, Jan 73 (796 ref.)**

HEART DISEASES

The many facets of cardiac pathology. Pomerance A. **Geriatrics 28:110-5, Nov 73 (31 ref.)**

HEART ENLARGEMENT

Cardiomegaly at high altitudes: pathogenetic considerations. Badeer HS. **Aerosp Med 44:1173-80, Oct 73 (98 ref.)**

HYPERTENSION

Hypertension, antihypertensive drugs and atherosclerosis. Hollander W. **Circulation 48:1112-27, Nov 73 (118 ref.)**

MYOCARDIAL INFARCT

Hypoxaemia in acute myocardial infarction. A discussion of its significance, causes and treatment based on data from the literature. De Geus A. **Neth J Med 16:222-9, 1973 (24 ref.)**

NOREPINEPHRINE

Uptake of noradrenaline by smooth muscle. Gillespie JS. **Br Med Bull 29:136-41, May 73 (69 ref.)**

* Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue (Amer J Cardiol 28: 366–967, 1971).

President's Page

It is with pleasure and satisfaction, but with a sense of overwhelming humility, that I shall attempt to fill the shoes so recently worn by Dr. H. J. C. Swan. They are big shoes—they were worn many miles for the College—and because they were worn by Dr. Swan the College is the better and has gained in stature and prestige on the scene of American medicine. The College shall always be in debt to Dr. H. J. C. Swan because he was President in 1973–74.

The restraints of journalism are such that this letter for the March issue of the Journal was due January 5. (At that time H. J. C. was still President and as President-Elect I was still able to "let him do it.") But it is not inappropriate that this first letter as President be composed on New Year's Day.

I am not a seer and cannot predict what will be our lot in March 1974. But on this New Year's Day one cannot help but be a bit concerned for the future. The year 1973 has seen the overwhelming vote of confidence in our national leadership vanish with the resignation of the Vice-President, who preferred not to contest the truthfulness of charges; the evidence that power might well have been ruthlessly used for no other purpose than acquiring more power; the decline of confidence in our chief executive on the domestic front despite rather remarkable accomplishments in some sectors of the international front. 1973 was a year in which the social and the political fiber of our country was stretched to and beyond the breaking point. If this was not enough, as a nation we were forced to recognize that we were no longer the master of our economy but that our purse strings could be controlled by others if for no other reason than military gains. These and other events prompted Jack Anderson to report in his syndicated column of January 1, 1974: "There is a strong feeling that it is up to the American people to bail the country out of its difficulties because the leadership in government cannot do it."

It is into the unknown of 1974 that I must wear the shoes of the President of the American College of Cardiology. When I turn them over in 1975 to the President Elect, Dr. Charles Fisch, they will be worthy of wearing only if you have helped during 1974.

In the past it has been proper for the President of a distinguished medical organization such as the American College of Cardiology to enunciate at the beginning of his term how the profession has been wronged and what he proposes to do about it. Future letters in the Journal shall be devoted to the personal problems of the College and its membership: Heart House, PSRO, third party payment, fellowship training, research support, and the like. But now is the time for bigger concerns—concerns outside our usual interests. Now is the time for physicians, for cardiologists, to think and act as citizens individually and collectively to provide the leadership this country so desperately needs.

The individual and collective freedoms that we have cherished and have grown accustomed to are being challenged. Now is the time for men and women of integrity, dedication, vision and good will to come to the fore and contribute to the betterment of their city, their state, their nation and their world. Since the founding of our country, physicians have assumed roles of leadership. If ever such leadership was needed, it is now. So I challenge the Fellowship of the College—the entire membership of the College—to think beyond their practice, their laboratory, their institution to their city, their state and their nation. I challenge the members of the College to identify something that they can do as citizens to assume leadership in community projects, right wrongs and set examples of decency and dedication. I give to you, as I gave to the College at the Convocation in New York, the challenge enunciated in 1960 by the late John F. Kennedy: "Ask not what your country can do for you but what you can do for your country."

The College is over 6,000 strong. Each member is a leader in his own right, but each was selected from many and is a physician because of the efforts and financial sacrifices of many; each owes a debt to society and now society is looking to its doctors for leadership. There is a time for doctors to be vocal about PSRO, HMO and Phase 4 restrictions, but I urge each member of the College to extend his interests and efforts beyond these personal concerns and look to the broader needs of society as a whole. For "there is a strong feeling that it is up to the American people to bail the country out of its difficulties because the leadership in government cannot do it."

Will you not dedicate yourself despite the pressures of practice, the laboratory and teaching to devote a bit of time each day to improving the lot of society as a whole in areas quite remote from medicine? If you do, the image of the College and of medicine will glow brighter in 1974 than it ever has before.

1974 will be a year of decision. Jack Anderson wrote, "Two sets of alternatives lie ahead of us. Decline can result in search either for scapegoats or self-knowledge. The collapse of illusions can bring either panic or maturity, the fall of idols either demoralization or resilience. Defeat can bring on a retreat into destructive egocentrism or a quest for a wider and truer communion."

Which will it be? Will the American people bail the country out? Knowing the membership of the College I know that we can, but will we? We can and we will if we devote our efforts beyond our own self-centered interests. We can and we will if we maintain the optimism of leaders in our College such as George Griffith who, when opening the William Likoff Symposium last December in New York, quoted William Allen White, and said "I am not afraid of tomorrow, for I have seen yesterday and am in love with today."

Henry D. McIntosh, MD, FACC
Houston, Texas

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

MARCH TO JUNE, 1974

MAR. 18–22 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Mt. Sinai Medical Center, New York, N. Y.

MAR. 21–23 **Core Curriculum: Pathology of the Heart.** Maurice Lev, FACC, and Jesse E. Edwards, FACC, directors. Palmer House, Chicago, Ill.

MAR. 25–27 **Electrocardiographic Interpretation of Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis, Ind.

MAR. 28–30 **High Blood Pressure—When and How To.** Robert S. Eliot, FACC, director. Gerald L. Wolf and Francis L. Land, co-directors. University of Nebraska Center for Continuing Education, Omaha, Nebr.

APR. 1–10 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 4–6 **Advances in Clinical Cardiology.** Lawrence S. Cohen, FACC, director and Alfred L. Aronson, William W. L. Glenn, FACC, Allan V. N. Goodyer, FACC, Norman S. Talner, FACC and Steven Wolfson, FACC, co-directors. Yale University School of Medicine, New Haven, Conn.

APR. 17–19 **Core Curriculum—Vectorcardiography (A Basic Workshop).** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

APR. 22–25 **Current Concepts in Cardiology—1974.** Philip R. Akre, director and John A. Bowers and Masato Takahashi, FACC, co-directors. MGM Grand Hotel, Las Vegas, Nev.

MAY 6–9 **The Recognition and Management of Coronary Syndromes.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 9–11 **The Ventricular Ectopic Beat: Heart-throb or Harbinger of Death.** Bernard Tabatznik and J. O'Neal Humphries, FACC, directors. Cross Keys Inn, Baltimore, Md.

MAY 15–17 **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director. Georgetown University School of Medicine, Washington, D. C.

MAY 17–19 **Core Curriculum: Rationa Drug Therapy in Cardiovascular Disease.** Robert J. Lee, PhD., director. The Nassau Inn, Princeton, N. J.

MAY 23–25 **Cardiologist's Appraisal o Operable Heart Disease.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors St. Francis Hotel, San Francisco, Calif.

JUNE 6–8 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

New Members Elected

The following individuals were elected to membership in the American College of Cardiology on November 5, 1973 in the category indicated.

FELLOWSHIP

ALLAN, Mary B., MD, Pennsylvania
AUER, James E., MD, Wisconsin
BARNES, Robert W., MD, Iowa
BAROLD, S. Serge, MD, New York
BECKER, Anton E., MD, Holland
BECKER, Lewis C., MD, North Carolina
BELCOURT, Christian L., MD, Canada
BERKOWITZ, Walter D., MD, New Jersey
BLOCK, Paul J., MD, New Jersey
BOIKAN, William S., MD, Illinois
BURMAN, Sheldon O., MD, Illinois
BURWELL, Lawrence R., MD, New York
CALVILLO-Juarez, Mario, MD, Mexico
CAMPION, Brian C., MD, Minnesota
CHAITHIRAPHAN, Suphachai, MD, New York
CHEUNG Chi-Shat, Anthony, MB, Hong Kong
CLAUSS, Roy H., MD, New York
CLINE, Robert E., MD, Texas
COCHRAN, Paul T., MD, New Mexico
DENTON, George D., MD, Canada
DODEK, Arthur, MD, Canada
DOTY, Donald B., MD, Iowa
DOYLE, Joseph T., MD, New York
EVANS, Roger W., MD, California
FITZ GIBBON, Gerald M., MD, Canada
FRIESINGER, Gottlieb C., II, MD, Tennessee
GANDER, Martin P., MD, California
GAULT, James H., MD, Pennsylvania
GLICK, Gerald, MD, Illinois
GRAHAM, Anthony F., MD, Canada
GRAHAM, Thomas P., Jr., MD, Tennessee
GROSSMAN, James I., MD, New York
GUINN, Gene A., MD, Texas
HAIDER, Riaz, MB, District of Columbia
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HARP, Vernon C., Jr., MD, California
HAWKINS, Harry M., Jr., MD, Oklahoma
HIROSE, Shigeru, MD, Los Angeles
HOFFMAN, Richard F., MD, California
HORWITZ, Lawrence D., MD, Texas
HUANG, Bernard L. N., MD, Massachusetts
HYMES, Alan C., MD, Minnesota
JOHNSON, Allen D., MD, California
JOHNSON, Lewis W., Jr, MD, New York
JOHNSON, W. Dudley, MD, Wisconsin
KATZ, Donald I., MD, New York
KHAN, Qamar A., MD, Tennessee
KHOO, Oon Teik, MD, Singapore
KOTLER, Morris N., MD, Pennsylvania
KREULEN, Thomas H., MD, Pennsylvania
LAGE, Raleigh H., MD, California
LASSER, Richard P., MD, New York
LEAMAN, David M., MD, Pennsylvania
LEE, Dixon A., MD, Maryland
LESHIN, Stephen J., MD, Texas
McCANN, William J., MD, New York
McDONALD, Charles D., Jr., MD, Tennessee
McGOWAN, Ronald L., MD, California
McNAMARA, J. Judson, MD, Hawaii
MAIR, Douglas D., MD, Minnesota
MANCHESTER, Joel H., MD, Pennsylvania
MANKIN, Harold T., MD, Minnesota
MANSUY, Matthew M., MD, Pennsylvania
MARTICORENA, Emilio A., MD, Peru
MEIJLER, Frits L., MD, Netherlands
OKUWOBI, Babasola, MB, Nigeria
OLLEY, Peter M., MD, Canada
PAINE, Robert, MD, Missouri
PARK, Sang C., MD, Pennsylvania
PATON, Bruce C., MD, Colorado
PATTERSON, Donald F., DVM, Pennsylvania
PEKAAR, Robert L., MD, Florida
PIERRE, Gerard D., MD, Haiti
REES, J. Richard, MD, Utah
ROBINSON, Norman J., MD, North Carolina
RODRIGUES, Rubem, MD, Brazil
SACKS, Jerome H., MD, California
SAHETA, Narayan P., MB, India
SENGUPTA, Ajit Nath, MB, India
SHINER, Philip T., MD, Virginia
SIEWERS, Ralph D., MD, Pennsylvania
STEWART, Samuel K., MD, Massachusetts
STINSON, Edward B., MD, California
TOMLINSON, John C., MD, Kentucky
TOSCANO Barbosa, Ely, MD, Brazil
TOWNE, William D., MD, Illinois
VARGO, Thomas A., MD, Texas
WALLOOPPILLAI, N. J., MB, Sri Lanka
WARSHAUER, Samuel E., MD, North Carolina
WATTS, L. Earl, MD, North Carolina
WEE, Albert S. T., MD, Singapore
WHITE, Richard S., MD, Utah
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WILSON, Charles S., MD, Nebraska
WILSON, Robert F., MD, Michigan
WINSLOW, Edward B. J., MD, Illinois
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BAHL, Om P., MB, Missouri
BASHOUR, Tali, MD, District of Columbia
BASSAN, Jacobo, MD, Panama
BEHAR, Victor S., MD, North Carolina
BULL, Marcia B., MD, Connecticut
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HARRIS, Clifford N., MD, California
HULL, Franklin E., MD, Michigan
KERBER, Richard E., MD, Iowa
LANDY, Ernest N., MD, New Jersey
LEVIN, Albert B., MD, Massachusetts
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MOOTS, Mark F., MD, Ohio
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NEMICKAS, Rimgaudas, MD, Illinois
PAREDES, August V., MD, Illinois
POMERANTZ, Barry, MD, New York
RAMIREZ, Alberto, MD, Massachusetts
REGNANTE, Richard M., MD, Massachusetts
RILEY, Charles P., MD, Florida
SHAH, Arvindkumar R., MD, Ohio
SHAH, Natverlal J., MD, India
SHECKET, Harman A., MD, Ohio
SINGH, Baikunth K., MB, India
SNOW, J. Allison, MD, District of Columbia
STENSON, Robert E., MD, California
THOMPSON, Mark E., MD, Pennsylvania

ASSOCIATE FELLOWSHIP

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BATTOCK, Dennis J., MD, Colorado
BELLO, Alexis G., MD, Venezuela
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CANNOM, David S., MD, Connecticut
CHEEMA, Mohan K., MD, New York
COLTART, D. John, MB, England
CORBIN, Murray David, MD, Kansas
DePALMA, Dominic M., MD, New York

* Elected May 22, 1973

FORRESTER, James S., MD, California
FOWLER, Jeffrey P., MD, Kentucky
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FUERTES, Antonio, MD, Texas
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GORDON, Richard F., MD, Florida
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HOFFMAN, Richard L., MD, California
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KARAYANNACOS, Panayotis E., MD, Ohio
KLUDGE, Wolfgang F., MD, Washington
LAVINE, Peter G., MD, Pennsylvania
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WATANACHAI, Kasem, MD, Illinois
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YOUNG, Guillermo A., MD, California

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FIERENS, Enrique E., MD, Michigan
FRANCIOSA, Joseph A., MD, District of Columbia
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GOEL, Brij G., MD, New York
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KLAUBER, John L., MD, New York
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* RAFAEL, Morad, MD, Illinois
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VYDEN, John K., MD, California
WINSTON, Burton, MD, California

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OMS-Rivera, Jorge D., MD, New York
PALACIO, Alfredo, MD, Missouri
PISUTHA-Arnond, Pornchai, MD, Illinois
RAMIREZ, Miguel A., MD, Mexico
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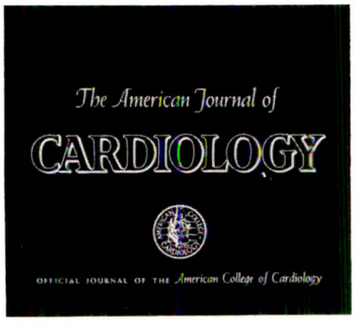

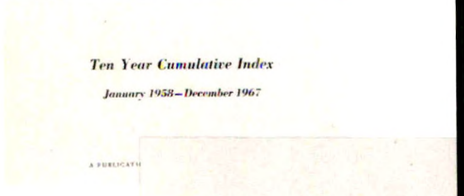

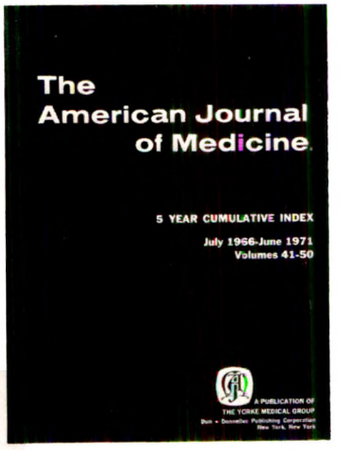

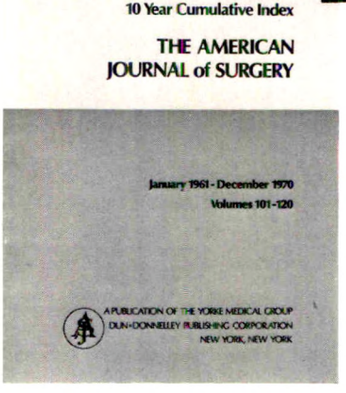

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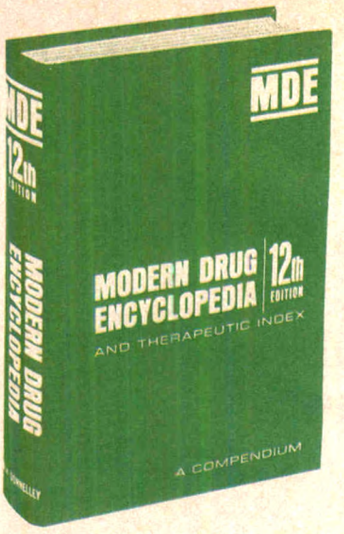

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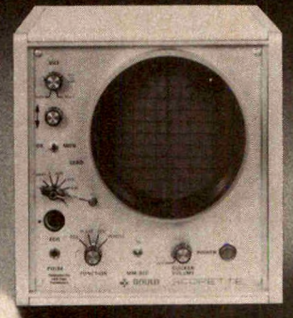

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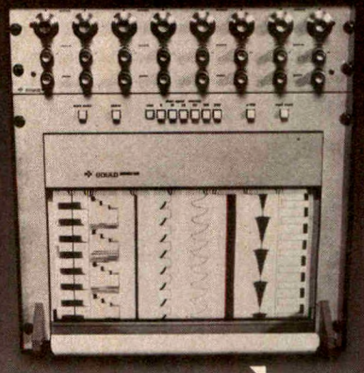

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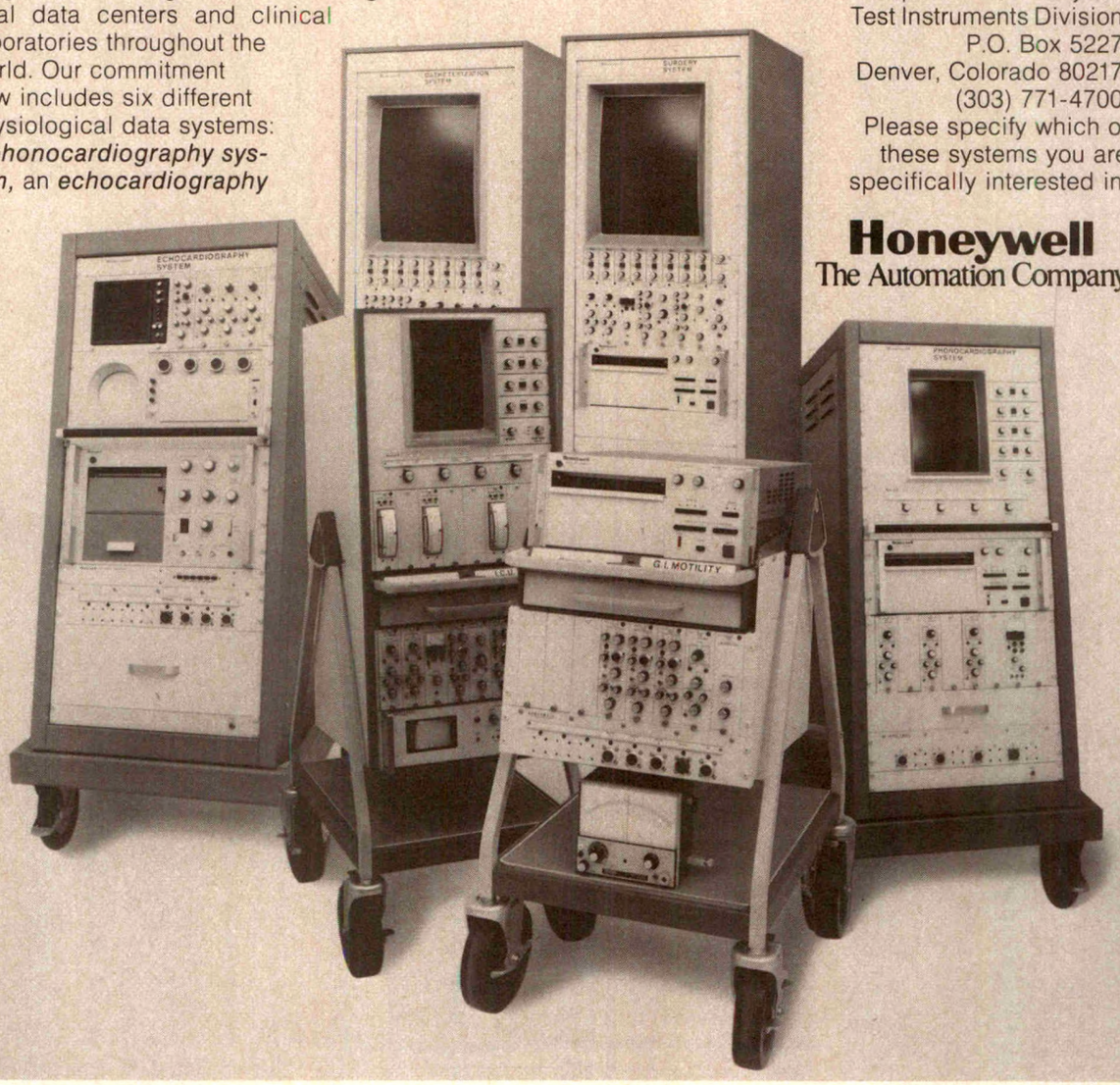
To get more information on the Honeywell biomedical systems mentioned above, please call or write: Peter Hamilton, Biomedical Products Department, Honeywell Test Instruments Division, P.O. Box 5227, Denver, Colorado 80217, (303) 771-4700. Please specify which of these systems you are specifically interested in.



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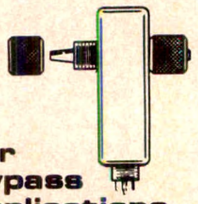

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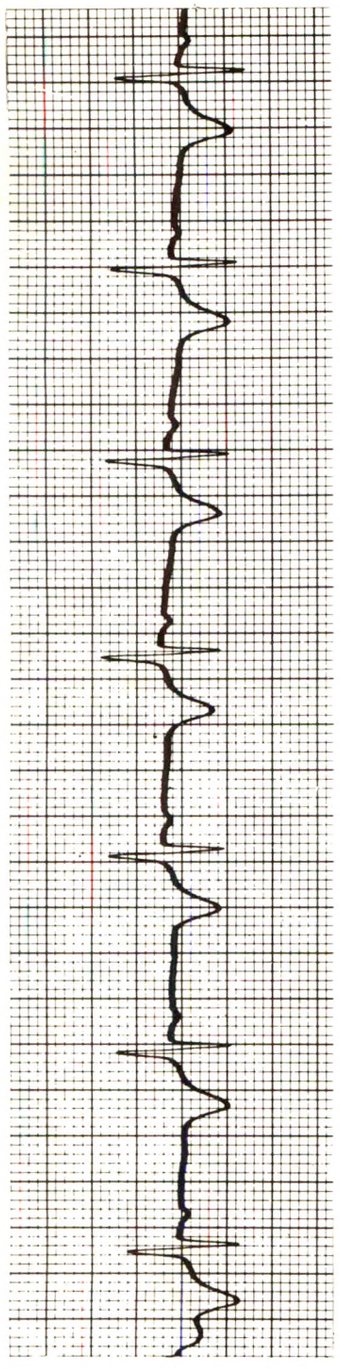

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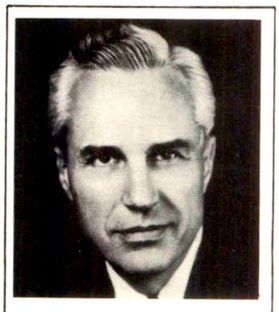

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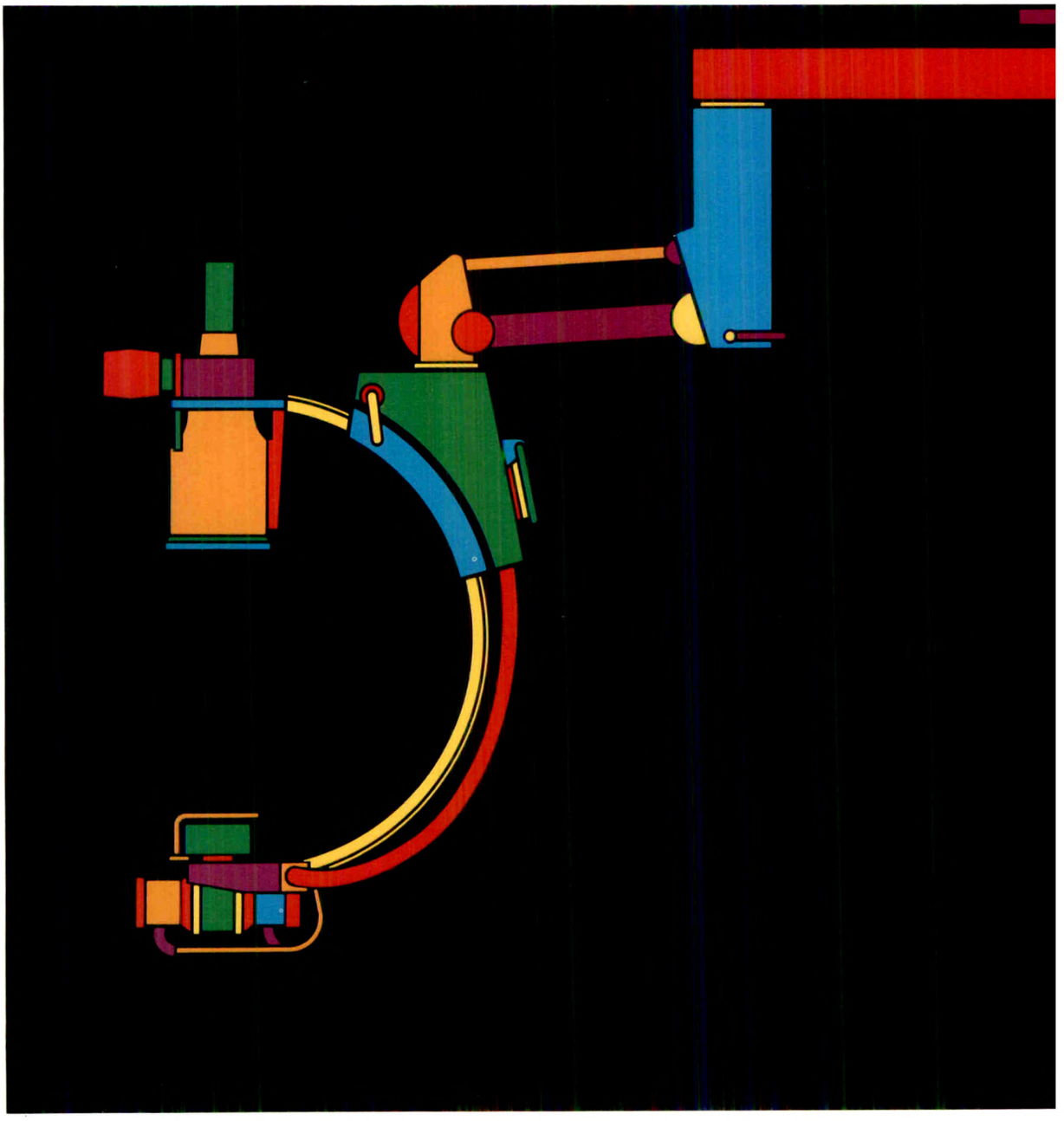

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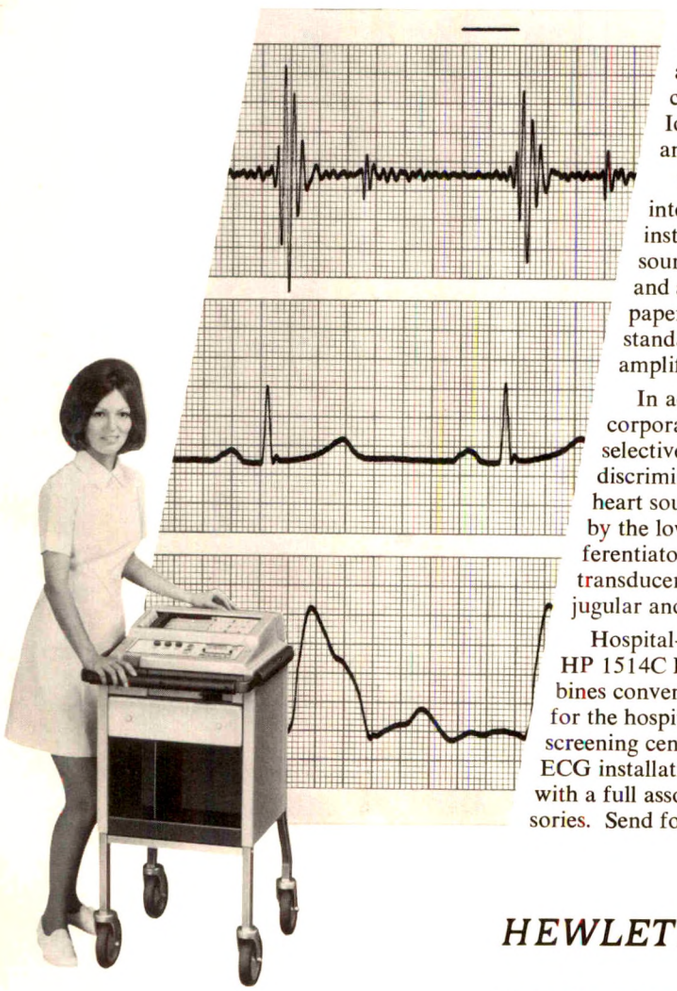

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AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

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COMPOSITION: Each 15 cc. (one tablespoonful) contains potassium chloride 1.5 Gm., supplying 20 mEq. of elemental potassium, in a cherry-flavored, palatable base, alcohol 4%. Contains no sugar.
INDICATIONS: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium or as a result of excessive vomiting and diarrhea.
CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
SIDE EFFECTS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
DOSAGE AND ADMINISTRATION: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
HOW SUPPLIED: One pint and one gallon bottles.

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APRIL 1974

The American Journal of CARDIOLOGY®

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Nitroglycerin in Acute Myocardial Infarction

Seattle Heart Watch

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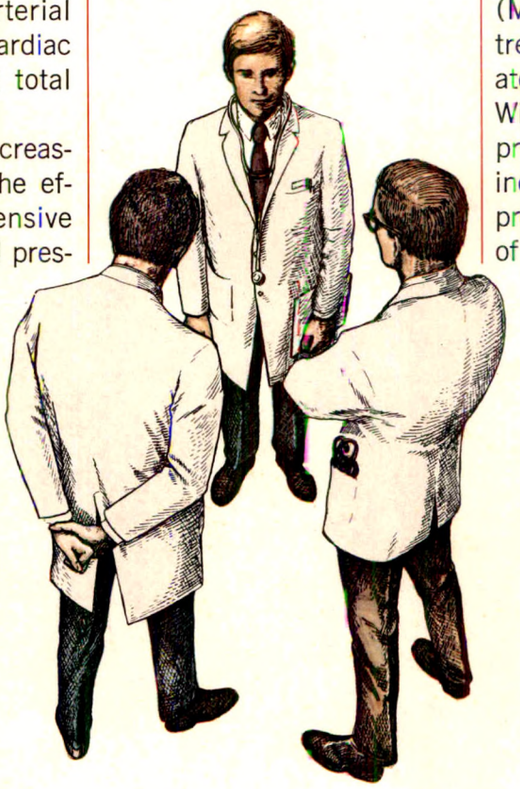
A YORKE MEDICAL JOURNAL

The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

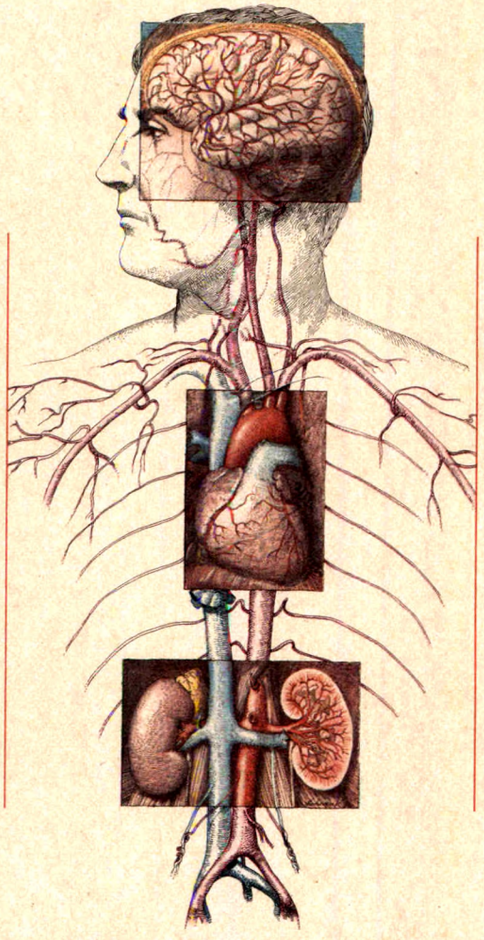
And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?



With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in

the more physicians rely on this unique antihypertensive



lowering blood pressure. But there are other considerations as well. Cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is actually slowed. Peripheral resistance is apparently reduced. ALDOMET does not usually compromise existing renal function; it generally does not reduce renal blood flow, glomerular filtration rate, or filtration fraction. And ALDOMET usually does not cause symptomatic postural or exercise hypotension.

Some patients on continuous methyldopa therapy may develop a positive direct Coombs test. For more details, see the brief summary of prescribing information.

Contraindicated in active hepatic disease and known sensitivity to the drug. Not recommended in pheochromocytoma or pregnancy. It should be used with caution in patients with a history of liver disease or dysfunction. Discontinue the drug if fever, abnormal liver function, jaundice, or acquired hemolytic anemia occurs.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

For a brief summary of prescribing information, please see following page.

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In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: Acquired hemolytic anemia has occurred rarely in association with therapy with methyldopa. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of the anemia. Rarely, however, fatalities have occurred.

Some patients on continued therapy with methyldopa develop a positive direct Coombs test; incidence reported has averaged between 10% and 20%. It rarely occurs in first six months of therapy, and if not seen within twelve months, is unlikely to develop with continued administration. Positive Coombs test is dose-related; lowest incidence occurs in patients on 1 g methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa. Prior knowledge of a positive Coombs reaction aids in evaluation of cross match for transfusions. Patients with positive Coombs tests at time of cross match may exhibit incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with blood otherwise compatible in the major cross match may be carried out. If positive, advisability of transfusion with blood compatible in major cross match should be determined by hematologist or expert in transfusion problems.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy in several patients with liver dysfunction has shown microscopic focal necrosis compatible with drug hypersensitivity. Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen; reversible agranulocytosis has been reported. Methyldopa may interfere with measurement of creatinine by alkaline picrate method and of uric acid by phosphotungstate method. When used with other antihypertensive drugs, potentiation of antihypertensive action may occur.

Usage in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Perform periodic hepatic function tests and white cell and differential blood counts during first six to twelve weeks of therapy or in unexplained fever. Discontinue if fever, abnormalities in liver function tests, or jaundice appears. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Discontinue drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Anesthetics requirements may be reduced; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension may occur after dialysis because methyldopa is removed by this procedure.

Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Do not exceed recommended daily dose of 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure, including dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency, are seen occasionally. Angina pectoris may be aggravated. Symptoms of orthostatic and exercise hypotension may occur; if symptoms occur, reduce dosage. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distension, constipation, flatus, and diarrhea occur occasionally; these can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently; if edema progresses or signs of pulmonary congestion appear, discontinue drug. Rarely, urine exposed to air may darken due to breakdown of methyldopa or its metabolites. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression, reversible thrombocytopenia, drug-related fever and abnormal liver function studies with jaundice and hepatocellular damage (see **Warnings** and **Precautions**), rise in BUN, and a single case of bilateral Bell's palsy.

Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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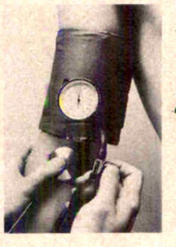
ADDENDUM

Let's make blood pressure "required reading" for all physicians.

With recent estimates that about 23 million Americans have high blood pressure—and that half of them are not even aware of it—detection of the problem in asymptomatic persons has become an issue of national importance.

Family physicians are being urged to take blood pressure readings as a matter of office routine, regardless of the presenting complaint or the reason for the visit. And because many people do not see a family physician for relatively long periods of time, some experts are suggesting that ophthalmologists, gynecologists, dermatologists, orthopedists, psychiatrists, dentists, school nurses, family planning counselors, and other health-care personnel make blood pressure reading a routine part of every examination or consultation.

Of course, a diagnosis of hypertension cannot be made on the basis of a single reading, but routine blood pressure readings can uncover potential trouble in a certain proportion of patients. And when trouble is suggested, further evaluation can be pursued more effectively.



Blood pressure—"required reading" for all physicians.

The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

while he's sleeping.

Quinaglute® Dura-Tabs® (quinidine gluconate) "a pharmacologic pacemaker":

- produces sustained serum quinidine levels, thus providing a convenient 8 or 12 hour dosage schedule
- usually insures uninterrupted therapeutic quinidine gluconate levels during sleep
- avoids peaks and valleys in plasma levels during which time the arrhythmias may recur
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- well tolerated to enhance patient cooperation—few G.I. disturbances

Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

Before prescribing or administering, please refer to QUINAGLUTE full product information.

Cooper Laboratories, Inc.
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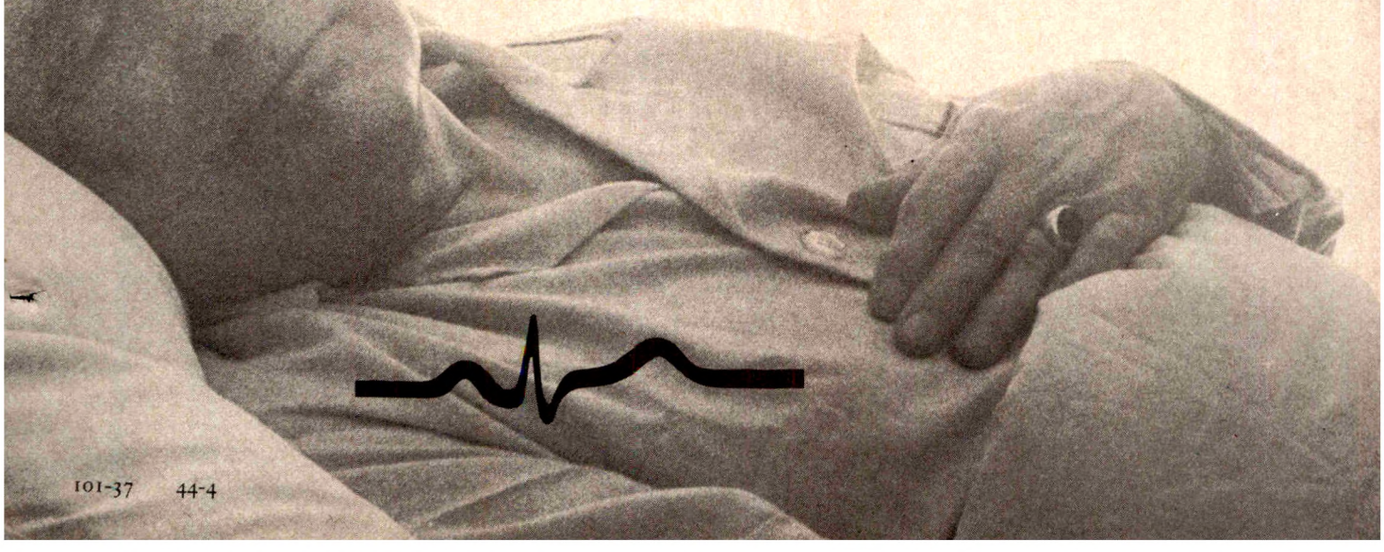
Quinaglute® Dura-Tabs®

(quinidine gluconate) 5 gr. (0.33 Gm.)

to help maintain the patient all through the night



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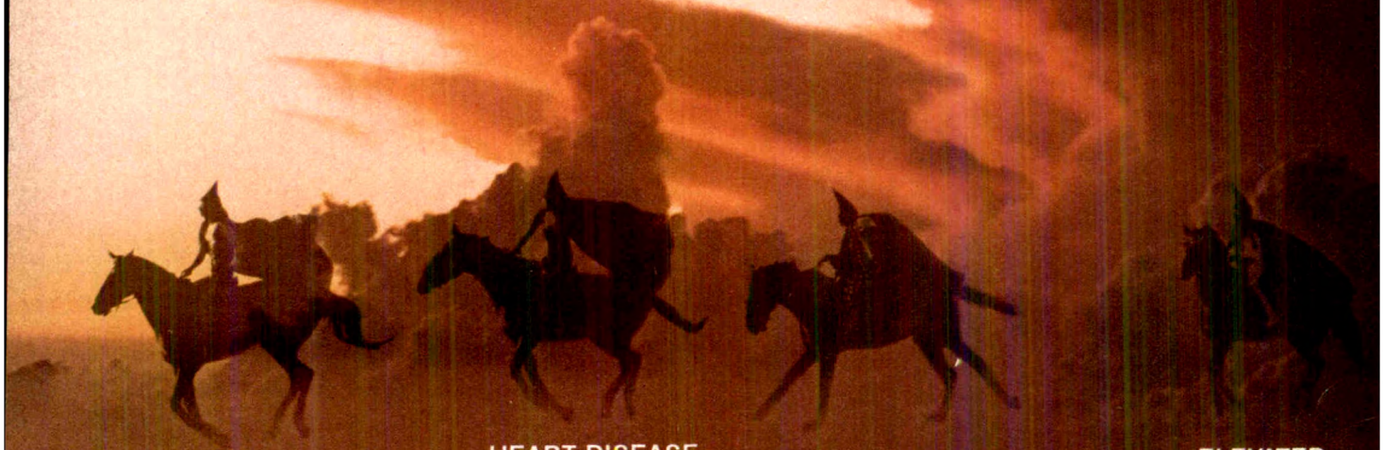
The Four Horsemen of Stroke...



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*Meyer, J. S., and Gilroy, J.: *Medical Neurology,*

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Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except September, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group, William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES: 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

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CLINICAL STUDIES

459 Seattle Heart Watch: Initial Clinical, Circulatory and Electrocardiographic Responses to Maximal Exercise

ROBERT A. BRUCE, GEORGE O. GEY, Jr., MANUEL N. COOPER, LLOYD D. FISHER and DONALD R. PETERSON

Frequency of future cardiac events (acute myocardial infarction and sudden death) after maximal exercise testing in 1,275 healthy men varied with age and risk assessment and in 1,057 patients with cardiovascular disease varied with diagnosis and natural history of disease. Computer-averaged S–T segment depressions were more consistent and reliable predictors than visual interpretations. In one patient testing caused postexertional cardiac arrest that responded promptly to defibrillation.

470 Electrocardiogram in Acute Pericarditis. Distributions of Morphologic and Axial Changes by Stages

DAVID H. SPODICK

Of 50 patients with uncomplicated acute pericarditis 48 showed classic stage 1 S–T segment deviations and stage 3 T wave inversions developed in 32. In the absence of stage 1 changes the electrocardiogram is ancillary to other evidence in diagnosing acute pericarditis, such as definite pericardial friction, inflammatory pericardial effusion or cardiac tamponade. Characteristic electrocardiographic lead and vector orientation changes are analyzed in these subjects.

475 Posterior Wall Velocity: An Unreliable Index of Total Left Ventricular Performance in Patients with Coronary Artery Disease

PHILIP LUDBROOK, JOEL S. KARLINER, ARNOLD LONDON, KIRK L. PETERSON, GEORGE R. LEOPOLD and ROBERT A. O'ROURKE

Echocardiographic determination of endocardial and epicardial posterior wall velocities in 48 patients admitted for diagnostic cardiac catheterization and coronary angiography correlated poorly with externally recorded systolic time intervals and other indexes of myocardial performance derived from cineangiograms. This technique does not provide reliable assessment of the total left ventricular performance in patients with ischemic heart disease.

483 Mortality in Patients Undergoing Coronary Artery Bypass Surgery After Myocardial Infarction

JOHN T. DAWSON, ROBERT J. HALL, GRADY L. HALLMAN and DENTON A. COOLEY

These data in 1,700 patients suggest that coronary artery bypass surgery can be performed 1 to 2 months after myocardial infarction without an increase in early mortality. In patients operated on within the first 7 days after acute infarction the mortality rate (38.1 percent) was more than six times greater than in patients operated on 31 to 60 days after infarction (5.8 percent). Emergency coronary artery bypass after complicated acute myocardial infarction should be reserved for those not responding to aggressive medical therapy.

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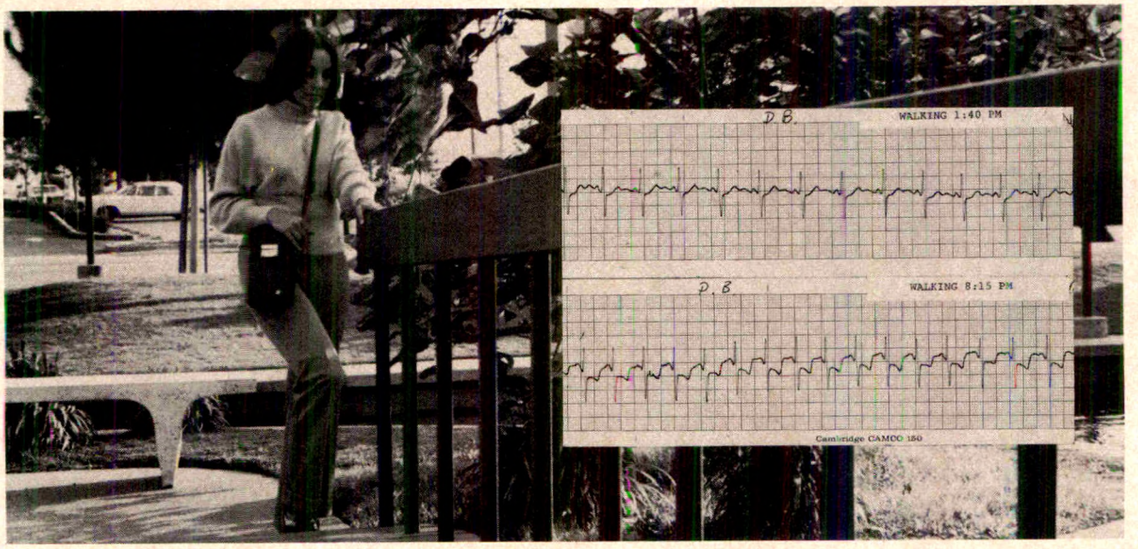

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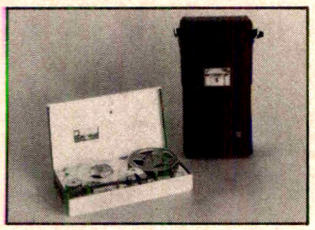

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487 Lidocaine-Induced Heart Block in Patients with Bundle Branch Block

PREM K. GUPTA, EDGAR LICHSTEIN and KUL D. CHADDA

The administration of lidocaine to 21 patients with intraventricular conduction abnormalities and ventricular premature contractions produced complete heart block distal to the His bundle potential in two patients and second degree block distal to the H deflection during atrial pacing in a third patient. These investigators advise caution in the use of lidocaine in patients with incomplete bilateral bundle branch block and consideration of a temporary pacemaker in patients with a prolonged H–V interval or known trifascicular disease.

493 Improved Intraventricular Conduction of Premature Beats After Diphenylhydantoin

JOE K. BISSETT, NEIL D. B. de SOYZA, JAMES J. KANE and MARVIN L. MURPHY

His bundle recordings and coupled atrial pacing were used to record the relative refractory period of the His-Purkinje system and the functional refractory period of the atrioventricular node in 14 patients before and after administration of diphenylhydantoin. The findings demonstrated that diphenylhydantoin significantly alters intraventricular conduction by decreasing the relative refractory period of the His-Purkinje system or reducing the H–V prolongation associated with aberrant conduction, or both.

498 Effect of Glucose-Insulin-Potassium Infusion on the Human Conduction System

LAWRENCE GOULD, C. V. REDDY and ROBERT F. GOMPRECHT

His bundle recordings in 21 patients with organic heart disease showed significant prolongation of the A–H interval after the administration of a glucose-potassium-insulin infusion. This study pinpoints potassium as the cause of the impaired conduction through the atrioventricular node and throws new light on the potential hazards of a potassium infusion.

507 Effect of Glucagon on Cardiac Conduction in Man

RAMESH C. DHINGRA, ASHFAQUE KHAN, DELON WU, PABLO DENES, J. MAURICE POUGET and KENNETH M. ROSEN

His bundle electrograms obtained before and after intravenous administration of glucagon in 4 patients with normal conduction and 22 patients with conduction disease revealed the following: Glucagon increased sinus nodal automaticity, as manifested by an increase in sinus rate and decrease of sinus nodal recovery time, and improved intraatrial conduction, as manifested by a reduction of the P–A interval and atrial functional and effective refractory periods. Glucagon had no effect on atrioventricular nodal or intraventricular conduction and did not appear to be arrhythmogenic.

EXPERIMENTAL STUDIES

513 Beneficial Electrophysiologic Effects of Nitroglycerin During Acute Myocardial Infarction

KENNETH M. KENT, ELDON R. SMITH, DAVID R. REDWOOD and STEPHEN E. EPSTEIN

Nitroglycerin enhanced the electrical stability of the heart during acute myocardial ischemia produced experimentally in open chest dogs. This beneficial electrophysiologic effect was probably related to reduction of ischemic injury and some action of nitroglycerin other than reduction in myocardial oxygen consumption mediated by decreased afterload.

Continued on page A15

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517 **Nitroglycerin-Induced Reduction in the Incidence of Spontaneous Ventricular Fibrillation During Coronary Occlusion in Dogs**

JEFFREY S. BORER, KENNETH M. KENT, ROBERT E. GOLDSTEIN and STEPHEN E. EPSTEIN

The effect of nitroglycerin on the incidence of ventricular fibrillation after coronary occlusion was studied in 27 open chest dogs. Twelve of the 13 control dogs died with ventricular fibrillation, whereas only 7 of 14 dogs treated with nitroglycerin died. The results indicate that nitroglycerin markedly diminishes ischemic injury, enhances ventricular electrical stability and significantly reduces the incidence of spontaneous ventricular fibrillation in an experimental model of acute myocardial infarction.

521 **Modification of Experimental Myocardial Infarct Size by Cardiac Drugs**

PRITPAL S. PURI

After coronary arterial occlusion in dogs, an intermediate zone of incomplete ischemia and partially diminished contractility was identified for the evaluation of the effects of various drugs on the extent of regionally ischemic myocardium. Isoproterenol initially augmented but later reduced contractility of this zone, whereas norepinephrine and ouabain produced consistent increases in contractility. Methoxamine increased left ventricular afterload, resulting in loss of contractility and its replacement by fiber lengthening in the intermediate zone. The data indicate that isoproterenol and methoxamine, unlike norepinephrine and ouabain, can increase the extent of noncontracting ischemic myocardium and, hence, infarct size.

529 **Pathophysiology of Tachycardia- and Bradycardia-Dependent Block in the Canine Proximal His-Purkinje System After Acute Myocardial Ischemia**

NABIL EL-SHERIF, BENJAMIN J. SCHERLAG, RALPH LAZARRA and PHILIP SAMET

In 18 dogs after acute myocardial ischemia produced by ligation of the anterior septal artery, differential localization of metabolites producing characteristic changes in the electrophysiologic properties of two groups of Purkinje fibers appeared to be responsible for the initial phase of tachycardia- and bradycardia-dependent block in the proximal His-Purkinje system. No relation was found between enhanced automaticity of pacemaker cells and bradycardia-dependent conduction disturbances.

METHODS

541 **Blood Flow Velocity Measured at the Mitral Valve of Man**

KENNETH B. DESSER and ALBERTO BENCHIMOL

The phasic mitral valve blood flow velocity pattern measured with the Doppler ultrasonic flowmeter catheter in 30 conscious human subjects consists of a large pandiastolic wave followed by a smaller systolic component. Deep inspiration decreases the peak mitral valve flow velocity; expiration increases it. A variety of other physiologic and abnormal states were studied.

REPORTS ON THERAPY

546 **Large Dose Furosemide Therapy for Hypertension. Long-Term Use in 22 Patients**

WILLIAM J. MROCZEK, MICHAEL DAVIDOV and FRANK A. FINNERTY, Jr.

This retrospective study of 22 hypertensive patients demonstrated that the combination of orally administered furosemide and standard antihypertensive therapy controlled high blood pressure better than other diuretic antihypertensive combinations previously used in these subjects. Large doses of furosemide may exert an additional antihypertensive effect, over and beyond the prevention of sodium retention and extracellular fluid volume expansion.

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heartblock; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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SAUL JARCHO

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JACQUES G. LOSMAN, HYMIE S. JOFFE, WALTER BECK and CHRISTIAAN BARNARD

In an 8 year old boy with an interrupted aortic arch associated with a ventricular septal defect and a large patent ductus arteriosus, the anomalies were totally corrected in one surgical procedure. The case provides another illustration of the significance of new pediatric surgical techniques in the prognosis for patients with congenital cardiac defects.

Continued on page A19

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Assurance that the recording is totally reliable depends, in part, on the quality of the chart itself.

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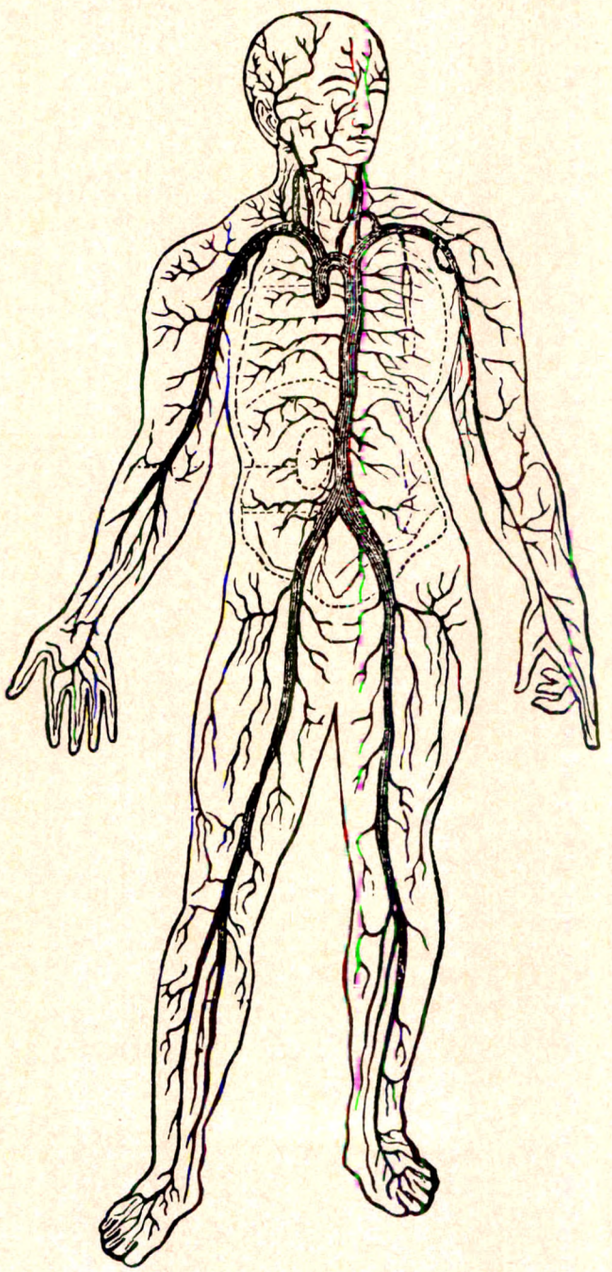

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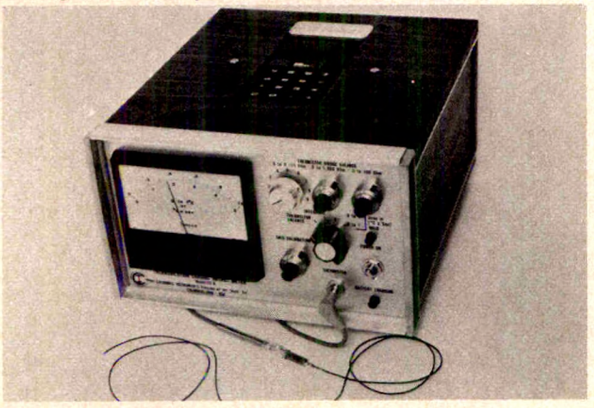

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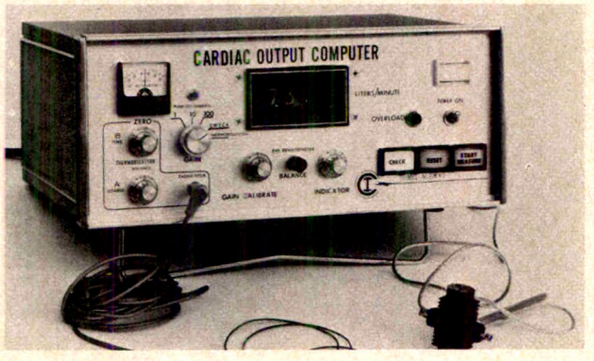

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(Procainamide Hydrochloride)

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 g. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

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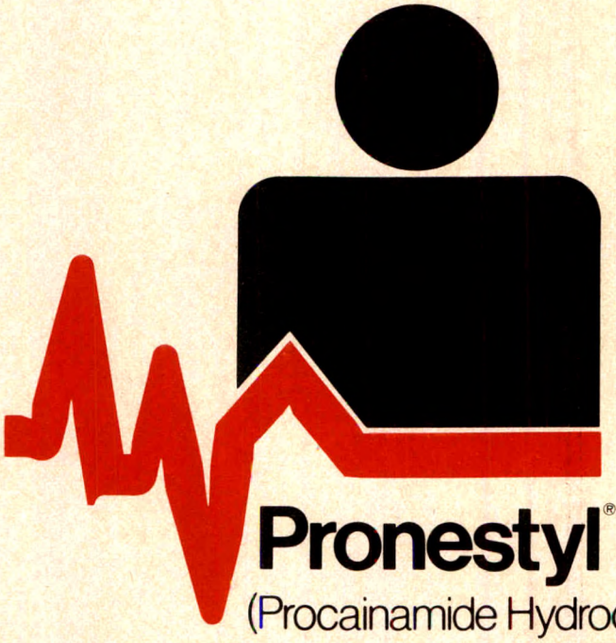

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(Procainamide Hydrochloride)

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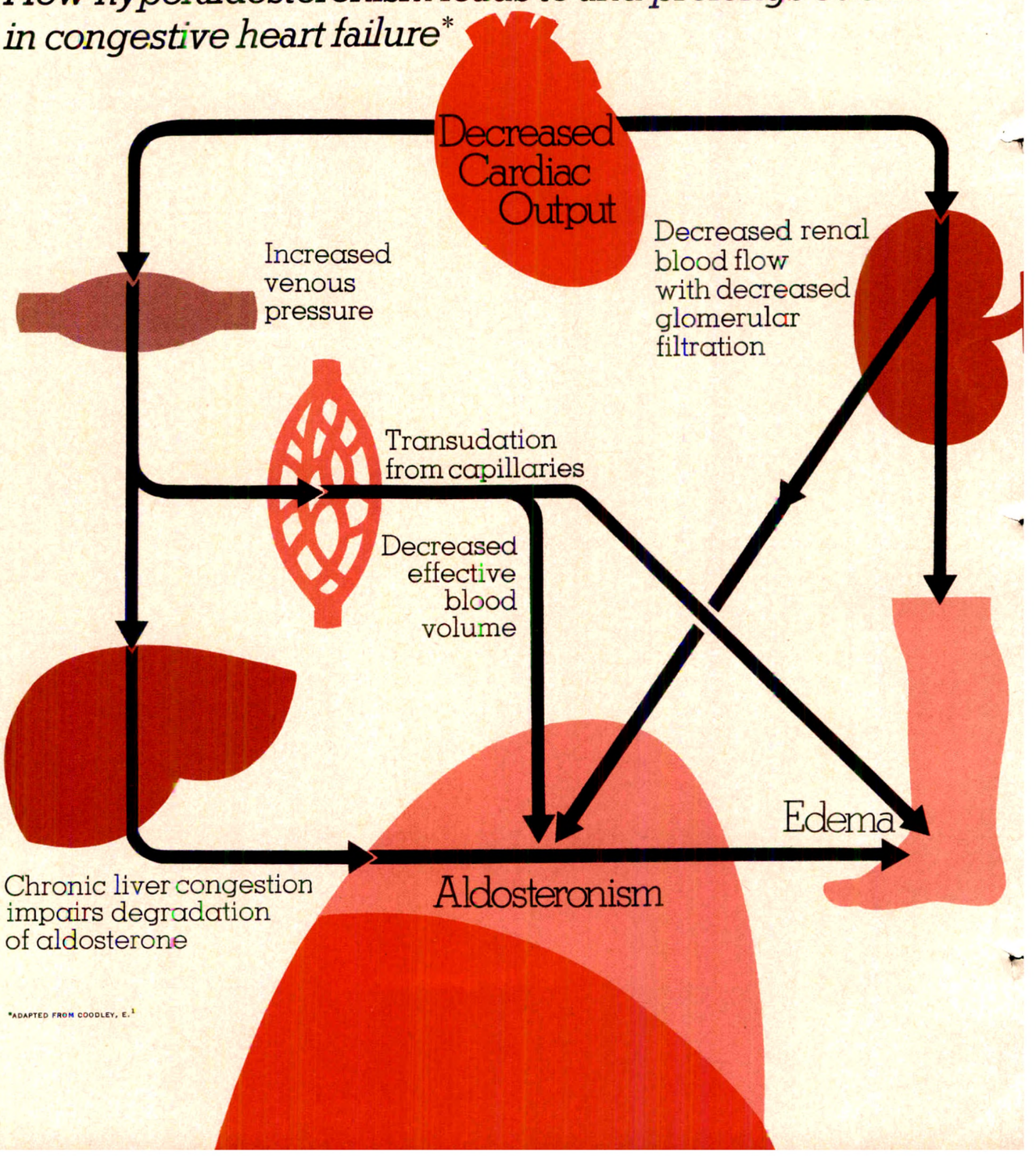
In congestive heart failure...

secondary aldosteronism

*How hyperaldosteronism leads to and prolongs edema in congestive heart failure**



*ADAPTED FROM COODLEY, E.[1]

is a primary factor

To "switch off" the aldosterone factor in congestive heart failure

Aldactone®

brand of

spironolactone 25-mg. tablets

the only specific aldosterone antagonist... basic in all diuretic therapy

Three ways to use Aldactone in congestive heart failure

1. As the only diuretic

- Often sufficient alone.
- Produces gradual, sustained diuresis by blocking aldosterone action in the distal renal tubule.
- Avoids potassium loss.

2. As the basic daily diuretic with an "add-on" alternate-day-diuretic ("A.D.D." schedule)

- Can be administered daily as basic therapy with the additional agent (furosemide or ethacrynic acid) given every second or third day.
- Aldactone plus "A.D.D." schedule minimizes potassium deficiency and potentiates effect of "add-on" diuretic.[2]
- Avoids acute volume depletion and aldosterone rebound.[2]

3. As a daily diuretic in combination with a daily dose of a thiazide

- Permits daily additive diuretic effect while maintaining potassium balance.

Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone (spironolactone), particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For **essential hypertension** in **adults** the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema, ascites or **effusions** in **adults** initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For **children** the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References: 1. Coodley, E.: Consultant 12:106-107, 109, 111, 113, 115 (July) 1972. **2.** Thorn, G. W., and Lauler, D. P.: Am. J. Med. 53:673-684 (Nov.) 1972.

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311

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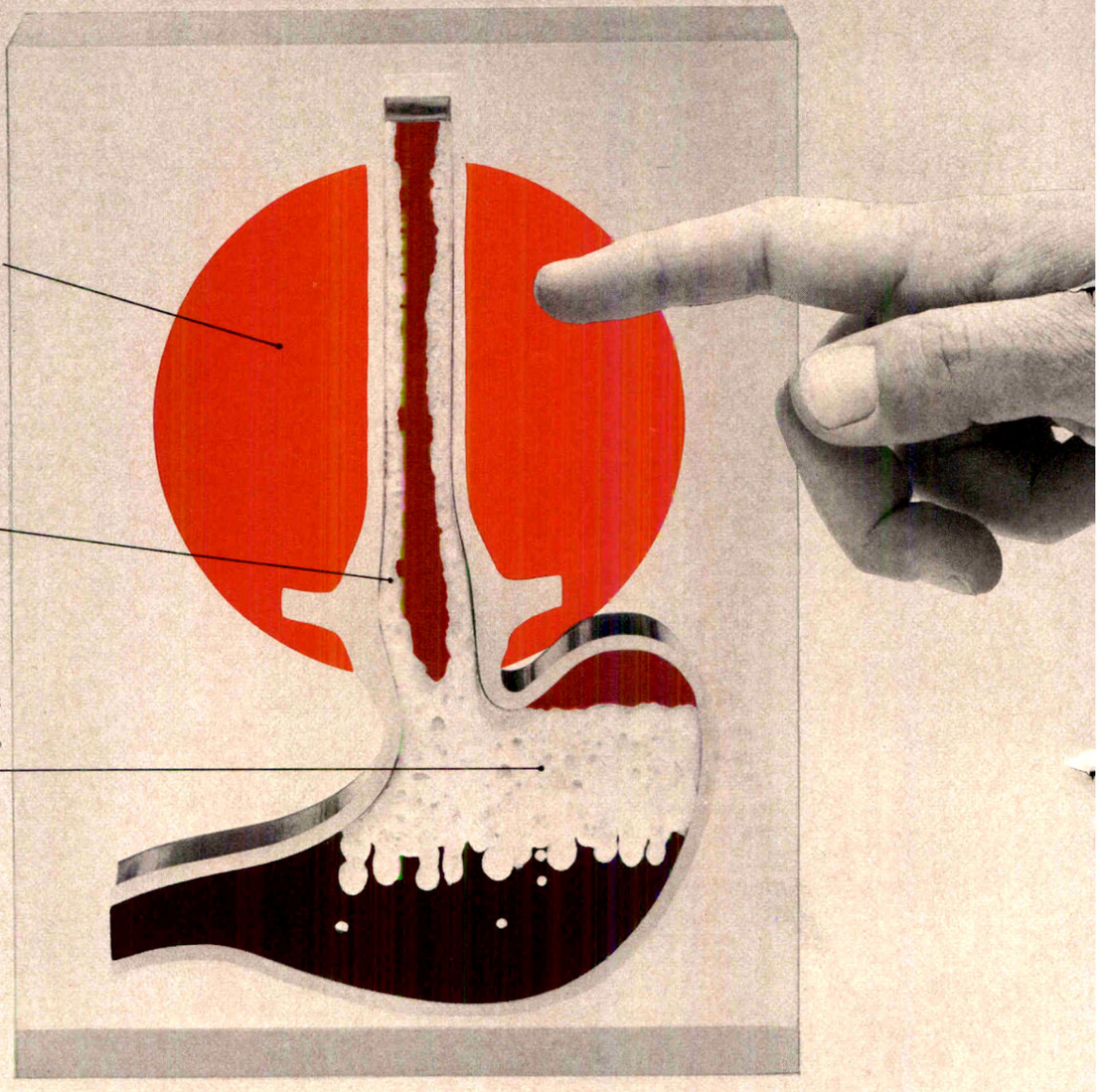

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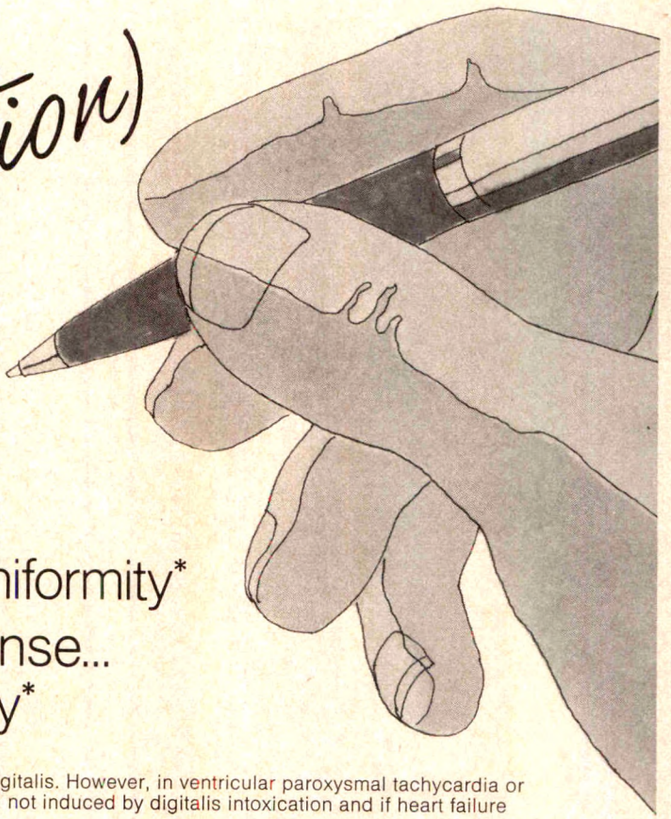

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precision quality control...
- assured tablet content uniformity*

predictable patient response...
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Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

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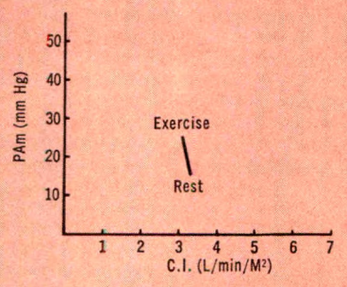
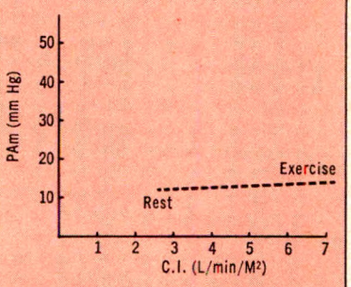
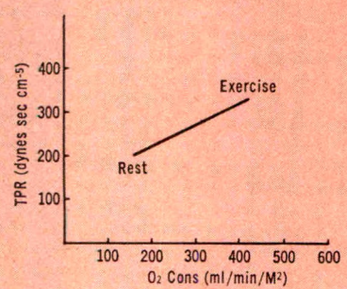
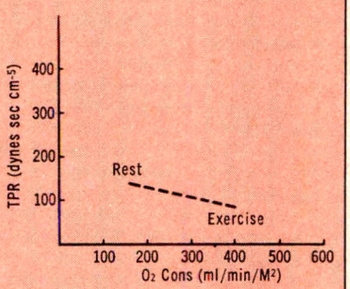
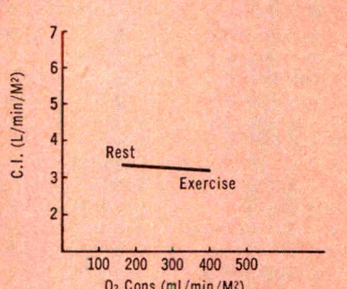
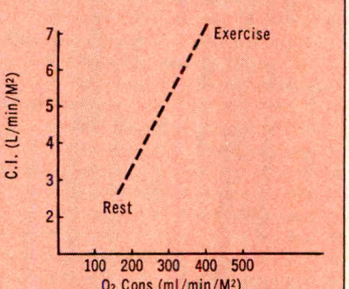
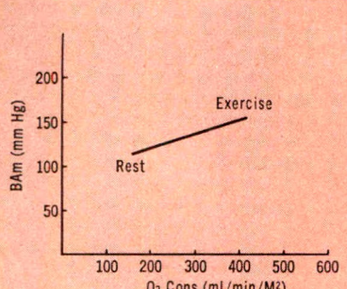
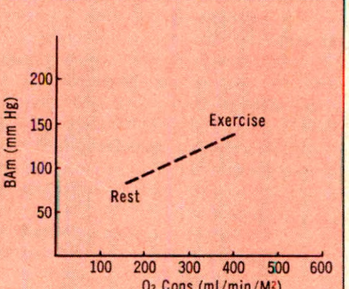
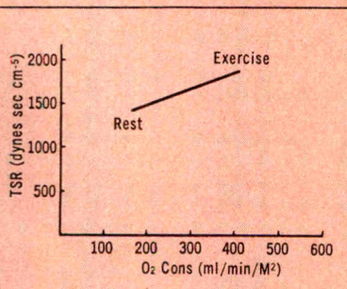
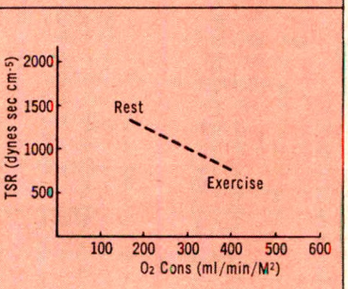
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

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"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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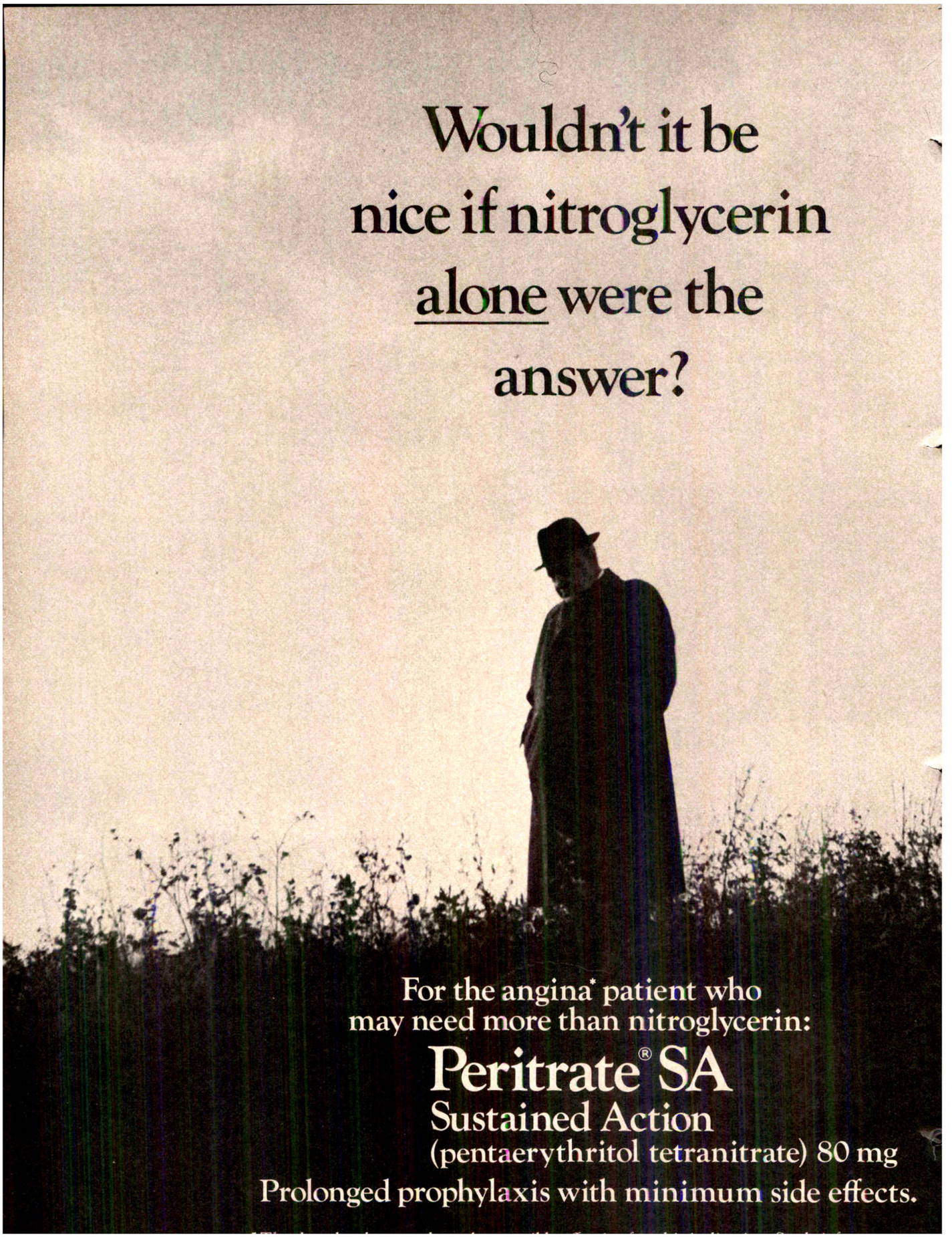
DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.


Wouldn't it be
nice if nitroglycerin
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answer?
For the angina* patient who
may need more than nitroglycerin:
Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80 mg
Prolonged prophylaxis with minimum side effects.

Peritrate® SA

Sustained Action (pentaerythritol tetranitrate) 80 mg

CAUTION: Federal law prohibits dispensing without prescription.

Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 and 1000.

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets; Peritrate 10 mg—light green, unscored tablets. Bottles of 100 and 1000. Full information is available on request.

Warner/Chilcott
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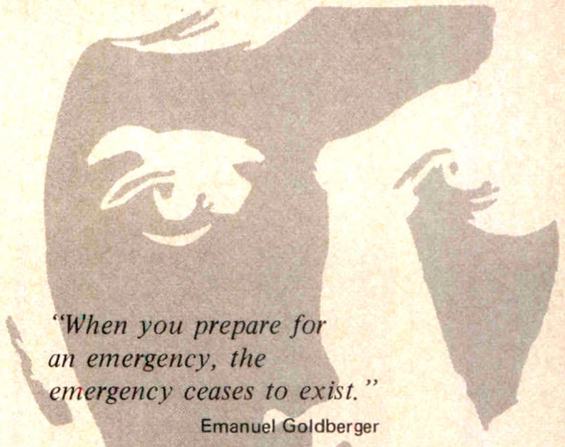
Morris Plains, N.J. 07950

PE-GP-41



"When you prepare for an emergency, the emergency ceases to exist."

Emanuel Goldberger

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THE TREATMENT OF CARDIAC EMERGENCIES

An unprecedented source for information on cardiac emergencies, this new volume emphasizes practical treatment and techniques designed to utilize available resources in the wide variety of settings where cardiac emergencies occur. Etiology, equipment, diagnosis, treatment and pharmacology of cardiac emergencies—all are concisely covered. A time-saving table of emergency treatments is included.

By EMANUEL GOLDBERGER, M.D., F.A.C.P.; chapter 13 by MYRON W. WHEAT, Jr., M.D. March, 1974. Approx. 424 pages, 7" x 10", 231 illustrations. About $14.00.

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This new edition begins with a combined discussion of etiology and prevention, then thoroughly examines modern treatment methods. New material on cardiogenic shock, arrhythmias, ventricular fibrillation, and pediatric resuscitation relate the latest corrective measures.

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This new volume focuses on possible complications involved with special radiographic procedures. It discusses each of the most common procedures in detail, delineating how to prevent complications and manage them should they occur. Legal implications are clearly presented.

By THOMAS F. MEANEY, M.D.; ANTHONY F. LALLI, M.D.; and RALPH J. ALFIDI, M.D.; with 15 contributors. May, 1973. 207 pages plus FM I-XII, 6¾" x 9¾", 51 illustrations. Price, $18.50.

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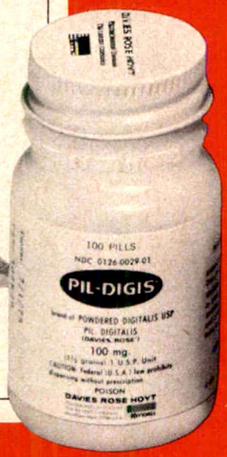

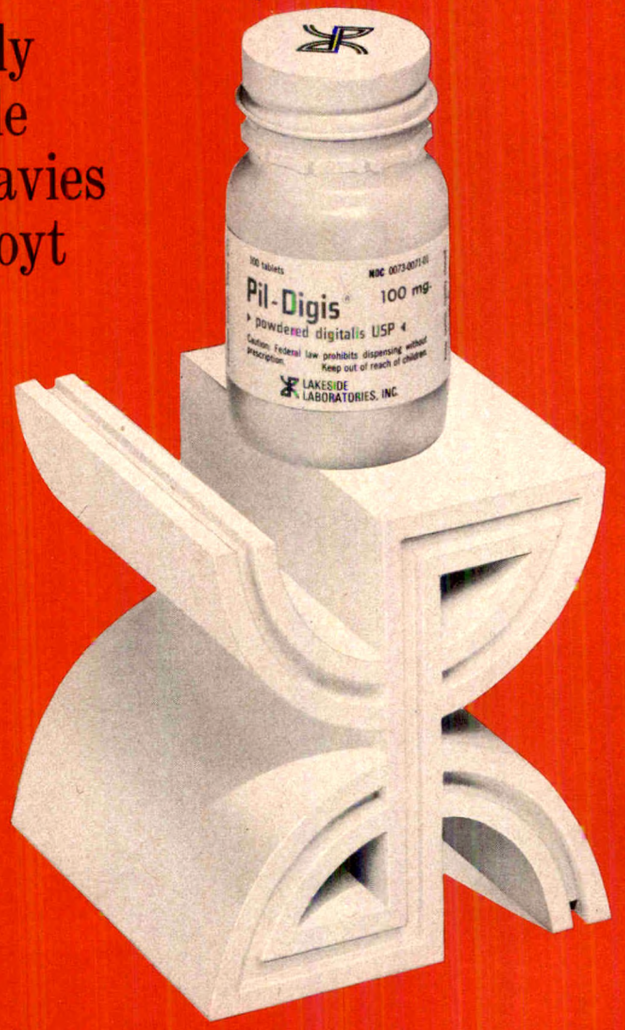

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DONTI™ The Pulmonary Performance Analyzer that makes every second count

Pulmonary testing is an important adjunct in the clinical handling of cardiac problems. In the few seconds required for a patient to perform a forced exhalation, the DONTI™ Pulmonary Performance Analyzer records and instantaneously displays a complete battery of sensitive spirometric parameters:

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With 10 more seconds of patient participation, the DONTI™ Pulmonary Performance Analyzer measures and expresses maximum voluntary ventilation (MVV) in liters per minute.

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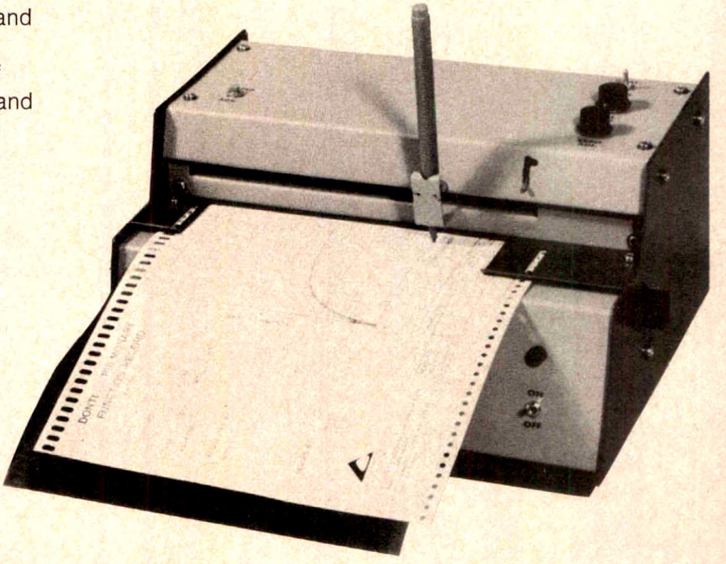
"The functional integration of the circulatory and respiratory systems makes it inevitable that disturbances in one will profoundly affect the other . . . lung complications constitute an important aspect of the diagnostic and therapeutic approaches to cardiac disease."[1]

In surgical handling of cardiac patients, the importance of preoperative pulmonary function testing has been noted. "Pulmonary complications developed after surgical operations in 70% of patients who had chronic lung disease; but in only 3% of those who had normal findings on pulmonary function tests and no respiratory symptoms."[2]

The compact Donti Pulmonary Performance Analyzer and Recorder can be used in the office or at bedside. Its electronic system simplifies the mechanical aspects of testing and allows the clinician to focus on the patient and test interpretation — with no diversion to preparing the instrument or to time-consuming calculations.



[1] Selzer, Arthur. Pulmonary Complications: The Other Side of the Coin. Medical World News *Cardiovascular Review/1973* pp. 83-84
[2] Stein, Koota, et al. Pulmonary Evaluation of Surgical Patients. *JAMA* 181:765-770, 1962

For bibliography and further information on chronic obstructive pulmonary disease, please write:

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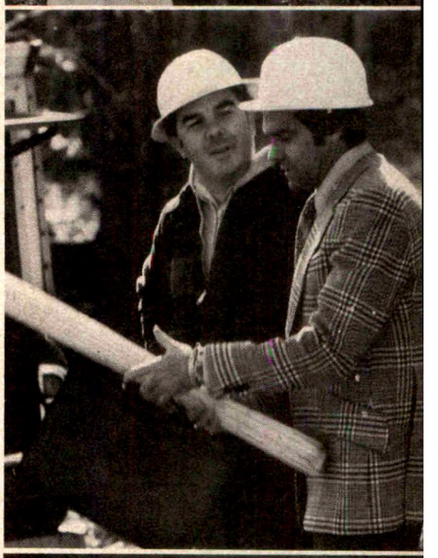
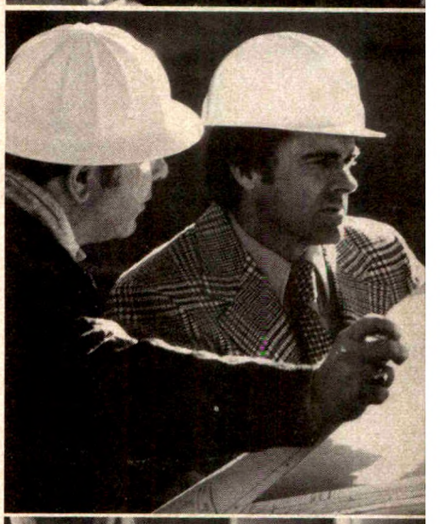
NEW FROM AYERST

the "healthy" hypertensive





It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

DIUCARDIN provides approximately the same diuretic potency as hydrochlorothiazide at maximal therapeutic dosage. With DIUCARDIN, the onset of diuresis is gradual and may be maintained for twelve hours or more with a single dose.[1,2] The antihypertensive effect of DIUCARDIN is usually maintained in long term use. For many patients on DIUCARDIN, a convenient once-a-day dosage may suffice.

Based on efficacy *and* economy, DIUCARDIN provides a good beginning for many hypertensive patients. New DIUCARDIN 50 mg. Tablets. For mild to moderate hypertension and adjunctive therapy for many types of edema. Ayerst®

controlled early on

Diucardin® TABLETS

(hydroflumethiazide)

diuretic/antihypertensive

(See prescribing information on next page.)

NEW FROM AYERST

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

diuretic/antihypertensive

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: **Hypertension:** DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN—No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

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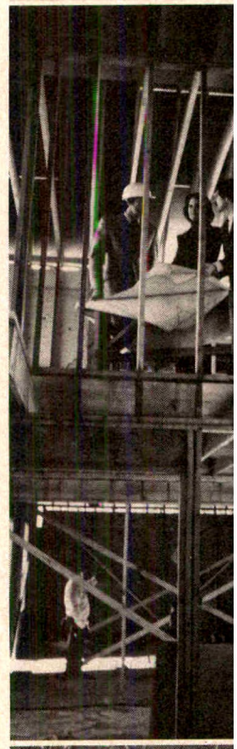

Thrombo-embolism

The Silent Threat

"Thrombotic phenomena now occupy first place as a complicating factor, if not the cause, of mortality as determined in all autopsy series in the United States today. Thrombotic disease has become an increasingly important cause of disability and death as infectious diseases have responded to chemotherapy and as public health measures have become increasingly effective."

Contributing to the seriousness of the problem is the fact that "At present there is no satisfactory technique for the recognition in man of the incipient or active thrombotic state."[1] There are, however, a number of factors which are known to predispose to thrombus formation and potentially fatal embolism. Recognition of these factors, plus the application of adequate prophylactic and therapeutic measures, could contribute significantly toward decreasing the morbidity and mortality caused by 'the silent threat.'

The population at risk

Although such modern techniques as isotopic lung scanning, the radioactive fibrinogen uptake test and the Doppler ultrasound flow detector show promise of permitting early detection of thrombus formation, it is generally agreed that these methods are not completely accurate as diagnostic tools, nor are they practical for large-scale patient screening. As a result, most physicians rely on the presence of known predisposing factors as a means of identifying patients who are especially prone to venous thrombosis and pulmonary emboli.

The high risk groups

As one authority has noted, these high risk "...groups include severely injured patients, particularly those over age 50 who have fractures of the pelvis, hip, or lower extremities; those undergoing elective cup arthroplasty or pelvic surgery; those immobilized or completely bedridden; those with a previous history of venous thrombosis or pulmonary embolism; those with severe obesity or congestive heart failure, or any combination of the above categories."[2]

Myocardial infarction: a special high risk category

Patients with acute myocardial infarction comprise another high risk group, especially if they have "...large transmural infarctions, previous infarction or angina, severe hypotension or shock, congestive heart failure, chronic atrial fibrillation, or past history of venous thrombosis or embolism."[2]

Therapy to lessen the risk

In patients with conditions known to predispose them to thrombosis and potentially fatal pulmonary embolism—the high risk groups—the use of anticoagulant therapy can be of significant benefit. As one investigator recently remarked: "If [the physician] believes that the risk of embolism is high he should use the only proved form of prevention, anticoagulation."[3]

With special regard to pulmonary embolism, it has been noted that "...a pulmonary infarct proves the existence of intravenous thrombosis and should be considered as a warning of possible further emboli. It is generally accepted that diagnosis of pulmonary infarction justifies the immediate application of anticoagulant therapy. Heparin is usually used initially, then oral anticoagulants (most commonly warfarin). The length of such therapy is often arbitrary, averaging four to six weeks, but depends on the extent and chronicity of the venous disease, whenever these can be determined."[4]

Myocardial infarction: a special case for longer term therapy

Following acute myocardial infarction patients are especially prone to such thromboembolic complications as mural and venous thrombosis and pulmonary and systemic emboli. The increased risk is due to reduced cardiac output, reduced arterial perfusion of the limbs, hypercoagulability (in the presence of cardiac ischemia), and venous pooling in the lower limbs—all of which may induce venous stasis leading to potentially fatal thrombus formation and embolization.

Because of the great risk of thromboembolic complications after myocardial infarction, anticoagulant therapy is widely recommended. As noted in a recent study, "...an excellent case can be made for the use of anticoagulants for the prevention of thromboembolic complications [following acute myocardial infarction]."[5]

With regard to duration of therapy, although there is no consensus, it is generally agreed that anticoagulants should be given for as long as observable benefits persist. In a study of 735 myocardial infarction patients treated with COUMADIN or another coumarin derivative: "Results indicate that anticoagulant therapy reduces the death rate significantly during the first three years after an acute myocardial infarction. However, survival rates converge after the third year, and by the fifth year there is no difference in survival of treated and untreated groups. Therapy appeared to be more effective in patients who had experienced more than one infarction. The incidence of recurrent infarction and congestive heart failure was less in the group treated with anticoagulants."[6]

Another investigator expressed his opinion on the duration of therapy by remarking that "...male patients on anticoagulants during the acute phase of myocardial infarction can logically be kept on them for 2 or 3 years when feasible. Such treatment can be recommended especially to men under age 55 and to men who have had a previous history of angina pectoris, myocardial infarction, or both, since they are the ones most likely to benefit."[2]

References:

1. Report of Inter-Society Commission for Heart Disease Resources, Sub-Committee on Thromboembolism, Wessler, S. (Chairman), *et al.*: Circulation *41*:A-31 (June) 1970.
2. Borden, C.W.: Med. Clin. North America *56*:235 (Jan.) 1972.
3. Browse, N.L.: New England J. Med. *287*:145 (July 20) 1972.
4. Selzer, A.: Medical World News: Cardiovascular Review, 1972, p. 88.
5. Ebert, R.V.: Circulation *45*:903 (April) 1972.
6. Ebert, R.V., *et al.*: JAMA *207*:2263 (Mar.) 1969.

COUMADIN®
(crystalline sodium warfarin*)

*present as crystalline sodium warfarin isopropanol clathrate

Please refer to brief summary of prescribing information on last page of this advertisement.

COUMADIN (crystalline sodium warfarin) BRIEF SUMMARY

EFFECTIVENESS: Coumadin® (crystalline sodium warfarin) is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

CONTRAINDICATIONS: Hemorrhagic blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms—cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities,** or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional block anesthesia.

WARNINGS: Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risk of hemorrhage due to anticoagulants is weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with increased risk of hemorrhage: **Pregnancy**—oral anticoagulants pass through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage *in utero*, even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. **Lactation**—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Severe trauma** of head, bones or muscles associated with extreme raw surfaces. **Surgery** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS: Periodic determination of prothrombin time is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinal; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; Coumadin® (crystalline sodium warfarin) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm./day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; Coumadin® (crystalline sodium warfarin) underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to Coumadin. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

ADVERSE REACTIONS: Potential side effects of Coumadin® (crystalline sodium warfarin) include: 1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.) Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc. 2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

TREATMENT FOR OVERDOSAGE: Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing Coumadin® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of Coumadin® (crystalline sodium warfarin) may suffice; and if necessary, small doses of vitamin K_1 (Mephyton®*) orally, 2.5 mg., will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 (AquaMephyton®*) in doses of 10 to 25 mg. may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.) Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of Coumadin® (crystalline sodium warfarin) administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level is readily obtained.

*Trademark, Merck Sharp & Dohme

For complete prescribing information, including dosage and laboratory control, see package circular.

SUPPLIED: Tablets: Coumadin® (crystalline sodium warfarin) for oral use, single scored, imprinted numerically with potency as follows: 2 mg. lavender, 2½ mg. orange, 5 mg. peach, 7½ mg. yellow, 10 mg. white, 25 mg. red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100. **Injection:** Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units, 50 mg.: Unit consists of 1 vial, 50 mg.; sodium chloride, 10 mg.; thimerosal, 0.2 mg. accompanied by a 2 ml. ampul Sterile Water for Injection. 75 mg.: Unit consists of 1 vial, 75 mg.; sodium chloride, 15 mg.; thimerosal, 0.3 mg. accompanied by a 3 ml. ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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COUMADIN®
(crystalline sodium warfarin*)

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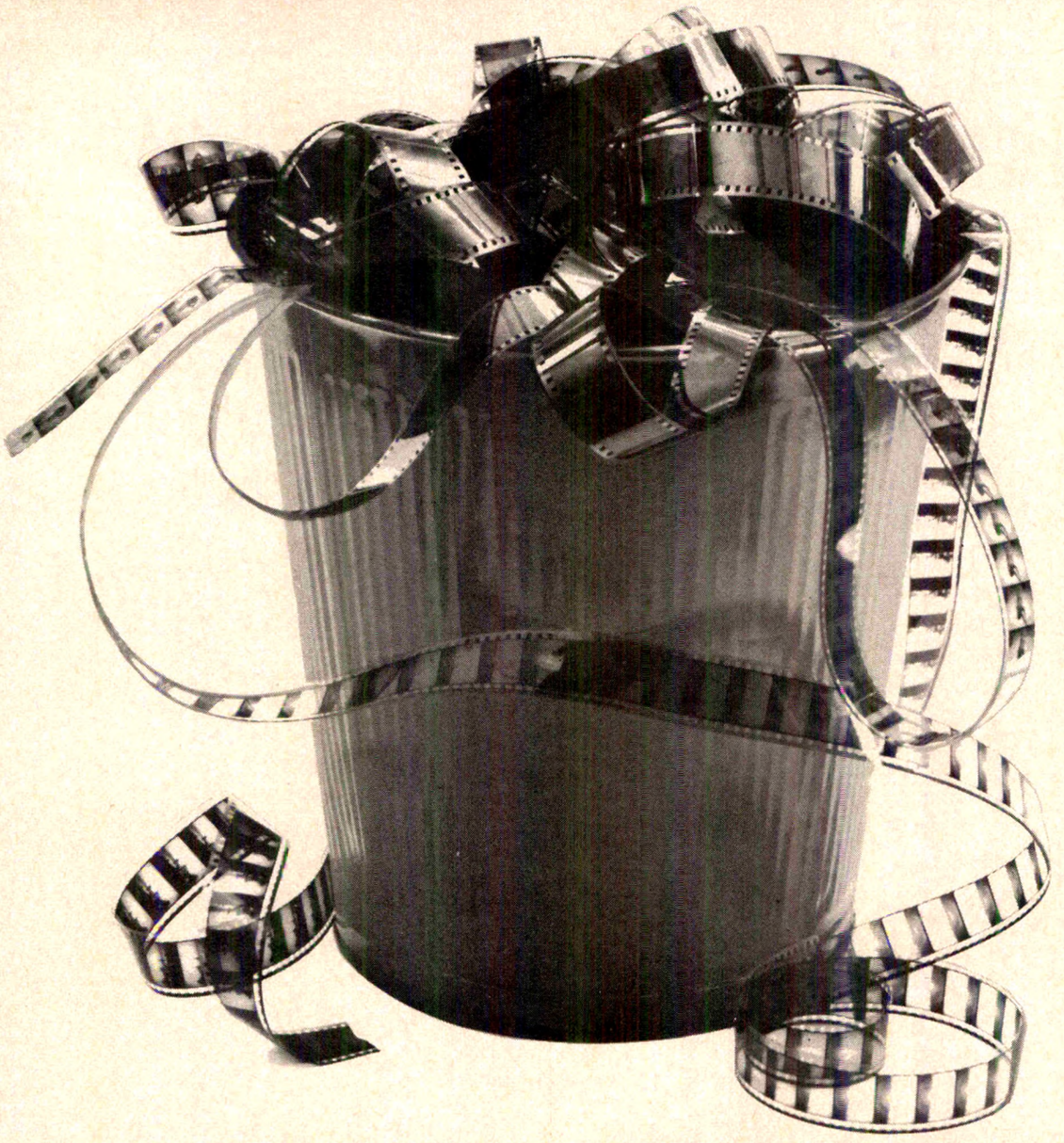

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A40

5
TRACK
a new
approach
in angina
pectoris...

Inderal®

Brand of

propranolol hydrochloride

beyond conventional measures and nitroglycerin

INDERAL, through a new mechanism, provides a unique approach in the management of patients with moderate to severe angina pectoris unresponsive to weight control, cessation of smoking, rest, sublingual nitroglycerin, and avoidance of precipitating factors. INDERAL should not be used in patients in whom anginal attacks occur only with considerable effort or infrequent precipitating circumstances.

decrease in anginal attacks and need for nitroglycerin

In 29[1-29] of 30[1-30] controlled clinical trials, INDERAL was found to reduce the incidence of anginal pain and the consumption of nitroglycerin. In 24[1-9,11-15,17,18,20-24,26,27,30] of these studies, it was possible to determine the proportion of patients responding to treatment; approximately 75 percent of the patients had less pain and used less nitroglycerin when taking INDERAL than when taking a placebo. Of the 29 studies reporting effectiveness with INDERAL, results were deemed statistically significant in 19,[1-19] not statistically significant in 2,[20,21] and the statistical significance was not given in 8.[22-29] In these and 3 other studies,[31-33] the effectiveness of INDERAL was demonstrated both clinically and by objective laboratory measurements. One study[30] reported propranolol not effective. Altogether, these clinical studies[1-33] covered 746 patients.

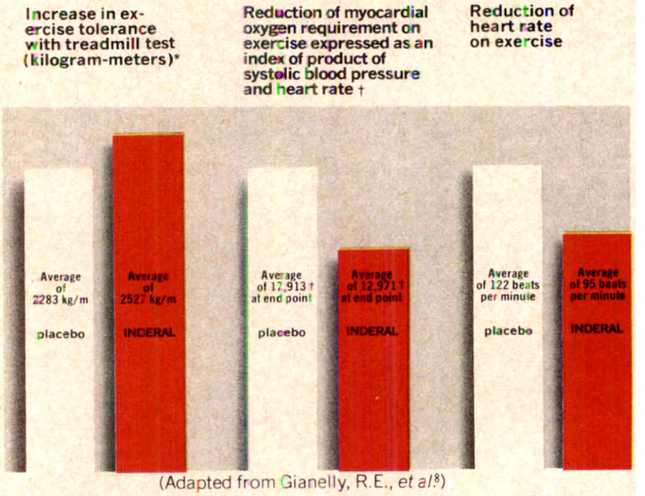
improved exercise tolerance

In 17 controlled trials dealing with exercise tolerance, INDERAL was found to be effective in 14[2,8,10,12,13,15,16,18,22,23,25,27,28,32] and not in 3.[3,29,30] In 8[2,8,10,12,15,16,18,32] of these, the improvement was statistically significant, in 6[13,22,23,25,27,28] the significance was not given.

objective proof of effectiveness

clinical results with 160 mg. Inderal (propranolol hydrochloride) daily in 19 patients

In a double-blind study, the effect of INDERAL on exercise tolerance was examined by Gianelly and associates.[8] It was concluded that in responsive patients,INDERAL, by reducing cardiac work, tends to bring into balance myocardial oxygen supply and need, and increases exercise tolerance.



(Adapted from Gianelly, R.E., *et al*[8])

*Incomplete data on one patient reduced the number to 18 for this aspect of the study.

In a double-blind crossover study of 19 patients with a typical history of angina and a positive Master 2-step test, the effects of INDERAL on exercise tolerance were correlated with cardiovascular physiologic effects. The patients, ranging in age from 38 to 65 years, received either placebo or 160 mg. INDERAL daily in 4 divided doses for 4 weeks. Exercise tolerance was assessed using a treadmill.

in the management of moderate to severe angina pectoris

works to decrease myocardial oxygen demand and prevent oxygen deficit in responsive patients

When physical or psychological stress increases beta-adrenergic stimulation of the heart, oxygen demand may exceed capacity for oxygen delivery in a coronary circulation compromised by atherosclerosis.

INDERAL (propranolol hydrochloride)—through its beta-adrenergic blocking action—provides a unique approach. By specifically competing with catecholamines for available myocardial beta-receptor sites, INDERAL can reduce sympathetically induced increases in heart rate, systolic blood pressure, and velocity of contraction during exercise or stress—and thus decrease the oxygen requirements of the heart. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to the decreased oxygen requirement.

for maximum effect, dosage should be titrated and individualized

The average optimum dosage of INDERAL appears to be 160 mg. per day, although individuals may respond at any dosage level. Starting with 10-20 mg. 3 or 4 times daily, before meals and at bedtime, dosage should be gradually increased at 3 to 7 day intervals until optimum response is obtained. Doses higher than the average optimum dosage of 160 mg. may be required; however, the value and safety of dosage exceeding 320 mg. per day have not been established.

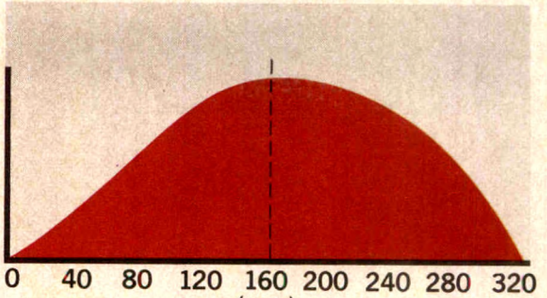
If treatment is to be discontinued, it is recommended that withdrawal be gradual over a period of several weeks. (See PRECAUTIONS.)

Special caution should be observed in patients with heart block or a history of congestive heart failure. (See CONTRAINDICATIONS and WARNINGS.)

Good medical practice dictates that INDERAL should not be continued unless there is reduced pain or increased work capacity. Treatment should be carefully monitored.

INDERAL will not interfere with the cardiac action of sublingual nitroglycerin, or cardiotonic agents such as digitalis.

average optimum daily dosage is 160 mg.



Clinical experience as reported in controlled studies has shown that the average optimum dosage appears to be 160 mg. per day. However, dosage must be individualized as some patients may obtain maximum response at a dosage level lower than 160 mg. daily, and others may require a dosage up to 320 mg. daily. The value and safety of daily doses of more than 320 mg. have not been established. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE OR EXAGGERATED RESPONSE)

USE OF **INDERAL® /ANGINA PECTORIS**
CONTINUED ON NEXT PAGE

(See last two pages of advertisement for prescribing information.)

Ayerst®

Inderal®

(propranolol hydrochloride)

for moderate to severe angina pectoris in responsive patients

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®

Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support or vital functional balances.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyro-

toxicosis, exercise).

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: *Angina Pectoris Due to Coronary Atherosclerosis.* The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL (propranolol hydrochloride) is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipatating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL (propranolol hydrochloride) should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, non-thrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg. three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. The value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See PRECAUTIONS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE

No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

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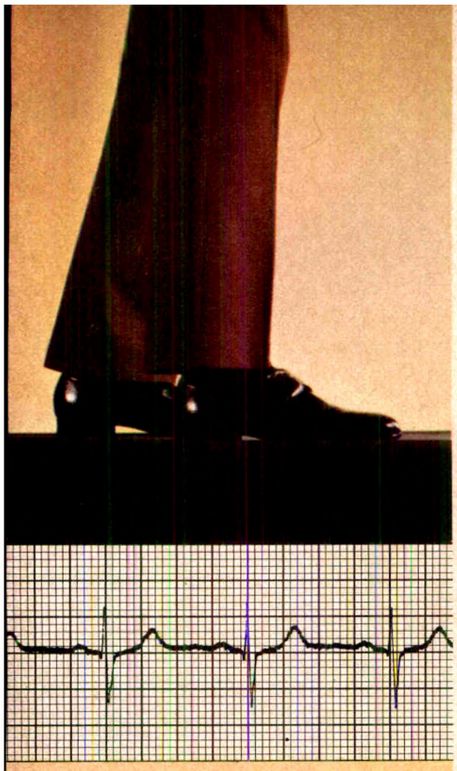
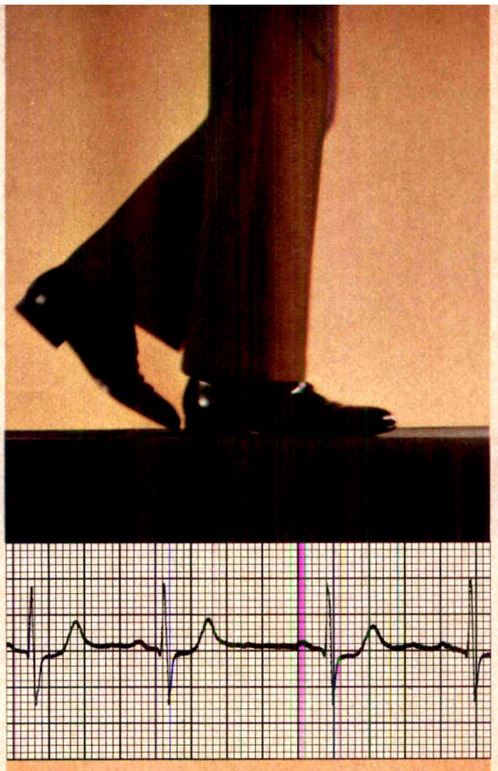


Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.

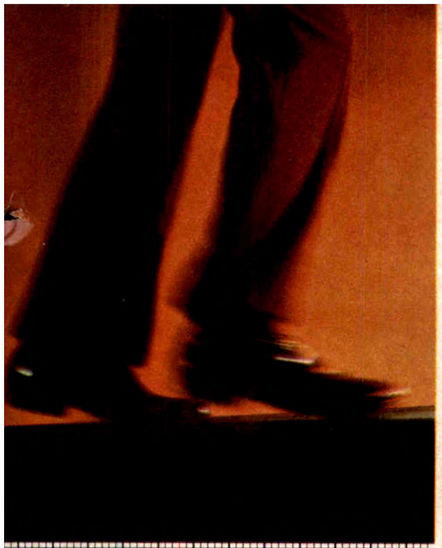


4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and impregnated foam pad which is slightly oversize to assure positive, continuous pressure at the electrode-skin surface. The results: immediate onset and virtual elimination of base line instability and motion artifact.

4th Minute at 3 mph (8th minute test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-T depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interference that might otherwise mask small amounts of S-T depression.

Finally.

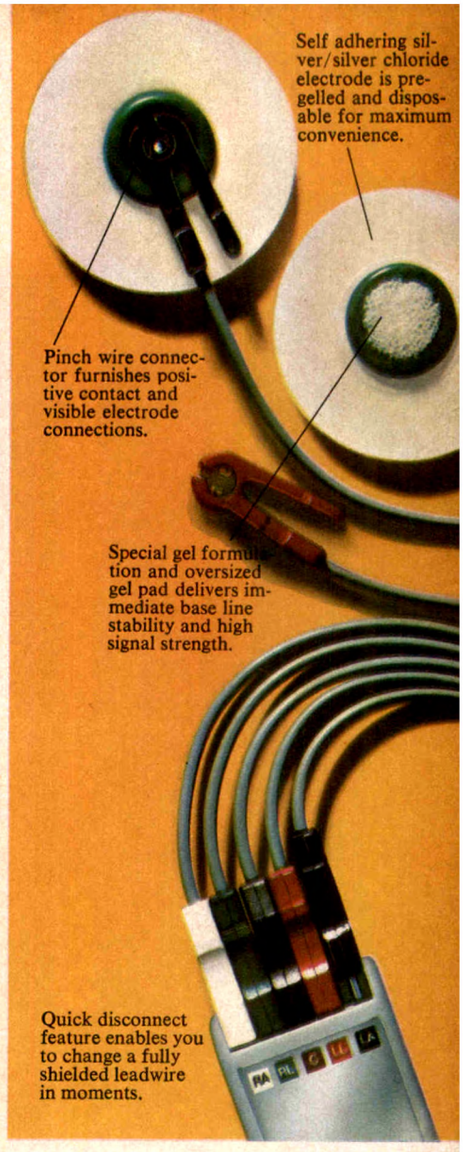
An electrode/cable system specifically designed for stress testing.



th Minute at 3 mph (12th minute f test), 5% Grade, V-5, HR-117. S-T depression increases to 2.5 mm.) Even at high work loads, the Ameri-an Stress Test Electrode and fully hielded cable system delivers a stable ase line and noise-free signal.

4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.) Long test procedures* seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

* Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's new Stress Test Electrode and fully shielded cable system.

If you've been diagnosing from stress test electrocardiograms that display wide or unstable base lines, severe motion artifact or possible hidden S-T depression, please contact us. We think we can help.

*Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

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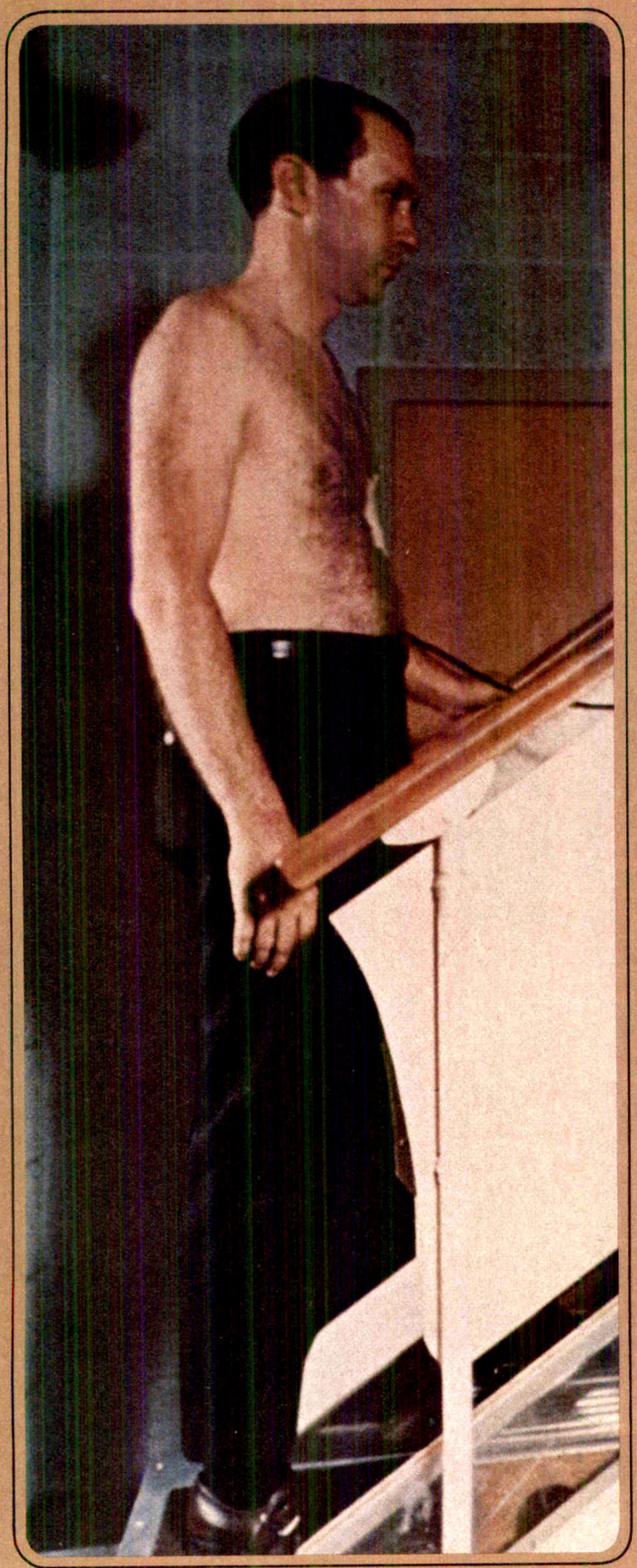

tolerance to exercise improved for angina patients

INDICATIONS: For the prophylaxis and long-term management of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

PRECAUTIONS: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

SIDE EFFECTS: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound.

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SUPPLIED: 10 mg. chewable tablets. Bottles of 100. Also 5, 10 and 15 mg. scored tablets in bottles of 100. 10 mg. scored tablets also supplied in bottles of 1000.

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APRIL 1974

The American Journal of CARDIOLOGY

VOLUME 33

NUMBER 4

CLINICAL STUDIES

Seattle Heart Watch: Initial Clinical, Circulatory and Electrocardiographic Responses to Maximal Exercise

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A network of 15 maximal exercise testing facilities in four teaching hospitals, 10 private offices and clinics and an industrial medical department was organized in July 1971 to study prospectively the antecedents of myocardial infarction and sudden cardiac death. Within 18 months 2,332 men were tested: 1,275 healthy "normal" subjects, 97 with prior myocardial infarction, 306 with angina pectoris, 193 with hypertension and 461 with various mutually exclusive combinations of these diagnoses; among these clinical groups were five patients who had had a prior episode of ventricular fibrillation. Historical, physical and laboratory data were recorded on self-teaching printed forms, with normal, borderline and abnormal responses arranged in three columns. Classification with respect to "unlikely," "questionable" or "likely" risk of future cardiac events was assessed from the highest tally of items in these columns. Analysis showed computer-averaged S–T segment responses were more consistent and reliable predictors than visual interpretations.

Cardiac manifestations in healthy men varied with age and risk assessment, and in patients with cardiovascular disease varied with diagnosis and natural history of disease. Many significant differences provided insights into mechanisms of impaired cardiac function in relation to type of clinical disease. Testing was responsible for one postexertional cardiac arrest. Recovery was effected promptly by defibrillation; there was no mortality.

From the Division of Cardiology, Departments of Medicine, Biostatistics and Epidemiology, University of Washington, and Boeing Medical Department, Seattle, Wash. This study was supported by Contract 71-2474 and Program Project Grant HL-13517 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. and an award from the Max Baer Fund of the Fraternal Order of Eagles. Manuscript accepted September 26, 1973.

The methods and initial results of maximal exercise testing received the "Third Award for Excellence" from the Board of Governors when exhibited at the 22nd Annual Scientific Session of the American College of Cardiology in San Francisco, February 15–17, 1973.

Address for reprints: Robert A. Bruce, MD, Department of Medicine, Division of Cardiology, University of Washington, Seattle, Wash. 98195.

"Candidates for future development of premature coronary heart disease can now be identified with a degree of probability unsurpassed for most other diseases, and equaled for a few." [1]

Effective prevention of cardiovascular morbidity and mortality in middle age requires earlier detection of hypertension and coronary artery disease. Once persons at risk are identified, clinical examination may indicate appropriate intervention to minimize the risk and to delay the occurrence of cardiovascular morbidity and mortality. Whereas examination at rest is sufficient to identify persons with consistently increased blood pressure, it is inadequate for early detec-

tion of coronary artery disease. Identification of risk factors such as hypertension, hyperlipidemia and cigarette smoking may be helpful,[1] but such factors are often absent in patients who experience myocardial infarction or sudden cardiac death.[2]* Epidemiologic studies indicate that postexertional S–T segment depression after moderate exercise is the most powerful predictor of future coronary events and is independent of the other risk factors, at least in men from the United States.[3] Preliminary comparative studies of postexertional S–T segment depression in healthy men observed repeatedly for 8 years indicate that, compared with the conventional double Master two-step test, the multistage treadmill test of maximal exercise is three times more accurate in predicting future coronary events.[4,5]

The Seattle Heart Watch was organized in 1971 as a prospective area practice study in order to elucidate the antecedents of acute myocardial infarction and sudden cardiac death.† The program comprises six units of study supported by a contract from the National Heart and Lung Institute and directed by Dr. Harold T. Dodge.

This report describes the organization and initial findings of only the exercise unit of the Seattle Heart Watch, which has two major purposes. The first is to define quantitatively the impairment of functional aerobic capacity and to identify some of the responsible cardiovascular mechanisms in each person tested. The second purpose is to test the experimental hypothesis that the risk of future cardiac events in a specific person may be predicted more accurately by use of maximal exercise testing than by assessment of risk factors identified by examining persons at rest. Differences in circulatory responses to maximal exercise with aging and with coronary disease have been described by Kasser and Bruce,[6] and representative limits of cardiovascular performance[7] and the assessment of functional aerobic impairment[8] have been reported elsewhere. This current study indicates the feasibility of applying these principles and these methods to an area practice in which a common protocol is used in several locations and electrocardiographic responses to exercise are relayed by dataphone to a central computer for quantitative analysis. Initial findings are described, and the feasibility of assessing subsequent morbidity and mortality is postulated. Validation of results must, of course, await the accumulation of adequate data on persons who have been followed up longitudinally for years.

Material and Methods

Case material: Subjects participating in this study include a group of ostensibly healthy executives and supervisors of the Boeing Company who have annual physical examinations and who have volunteered for this type of exercise testing. Other healthy persons from the Seattle area are being enrolled when they undergo a routine physical examination by their private physician. Also enrolled are patients classified in "clinical" groups as follows: (1) those with new or recent cardiovascular symptoms reporting to their physician for an initial diagnosis; (2) those known to have advancing symptoms of coronary artery disease who are being considered for surgical treatment of stable angina pectoris or other complications of coronary artery disease; and (3) a small number who previously have been resuscitated from sudden cardiac arrest, whether or not it was associated with myocardial infarction.

In the first 18 months of this study 2,332 men and 225 women were enrolled and their data entered into a computer file. For the purposes of this report, only the results from the men are presented, organized according to preliminary clinical classification (before exercise testing) into eight mutually exclusive groups. The number of men in each diagnostic category is listed in Table I together with the number of those who were previously resuscitated from sudden cardiac arrest* or who were studied by coronary arteriography.

Protocol: Many physicians and cardiologists were invited to participate in the organization of this prospective study. Each agreed to use the standardized protocol for the multistage test of maximal exercise,[7] provide a treadmill, electrocardiograph and defibrillator (for reasons of safety), submit bipolar precordial electrocardiographic signals by dataphone, and record data on standardized forms and submit them to the central laboratory. Each physician signed an agreement to follow these principles and to make no additional charge to his patients for extra computer analysis and data processing. The National Heart and Lung Institute contract supports the rental charges for dataphones and the costs of private telephone lines, computer processing, registration and the additional medical and nursing staff required for exercise testing of healthy persons in industry. A form used to obtain informed consent also gives each subject the physician's initial clinical appraisal of the presence of heart disease before exercise testing is performed. The diagnostic alternatives are termed "inapparent," "possible," "probable" or "definite" heart disease, to which are added any clinical notations as to major manifestations of disease and current treatment. This signed consent form documents each participant's enrollment into the Seattle Heart Watch and includes his consent to future follow-up studies. The experimental design, protocol, data forms and especially the informed consent statement were extensively reviewed and approved by the Biomedical Sciences Review Committee of the University of Washington. Testing laboratories have been established in four teaching hospitals, 10 private offices and

* In such cases they may be considered 'false negatives' and defined as "100 percent minus reported sensitivity of one or more predictive variables," that is, the relative importance of false negative findings, given the occurrence of a cardiovascular event. For increased serum cholesterol in men aged 40 to 59 years, this value is 73 percent; for either or both a systolic blood pressure of 160 mm Hg or a diastolic pressure of 95 mm Hg or more, it is 82 percent; for both increased cholesterol and blood pressure it is 89 percent, but for either or both it is 32 percent; for two or three risk factors it is 77 percent; for three risk factors 66 to 72 percent in different age groups and population studies; and for four risk factors 86 percent (Tables 2 to 5 and 7 to 10, Reference 2).

† By design, selection and sampling, the Seattle Heart Watch does not represent an epidemiologic study of a defined population. However, the principle of automatic, periodic follow-up surveillance is adapted from conventional epidemiologic practices.

* The number of men who underwent successful defibrillation by Medic I and were subsequently enrolled into Seattle Heart Watch after exercise testing are included in the subtotals for the various clinical classifications.

clinics in Seattle and the Boeing Medical Department (Renton plant).

Exercise data collected from all 15 participating groups are reported on standardized printed forms.* Physiologic data, such as change in heart rate from rest to maximal exertion, are scored by predetermined tolerance limits from a prior study of healthy middle-aged persons.[6] Data are arranged in three columns to facilitate assessment of risk, with normal responses (previously identified from other studies)* printed on the left side, abnormal responses on the right, and questionable responses in the center. Numerical data are recorded by a technician, and clinical items are checked by the supervising physician who monitors the

* Copies available on request to Dr. Bruce.

* Tolerance limits were defined from the best straight line fit to a cumulative percentage distribution of curves (smoothed by computer) of each continuous variable; they represented a close approximation (varying with any skewness of the distribution) to the mean ± 1.5 standard deviations and ranged from 81 to 90 percent of the normal samples for men and women.

TABLE I

Characteristics of 2,332 Men

	Healthy	HT	PMI	AP	PMI & AP	PMI & AP & HT	HT & AP	HT & PMI
Number of subjects by diagnosis*	1,275	193	97	306	228	75	138	20
Physical characteristics (means ± SD)								
Age (yr)	44.5 ± 7.4	49.3 ± 8.7	50.3 ± 8.3	51.2 ± 8.4	51.9 ± 8.0	51.5 ± 7.4	53.1 ± 7.0	52.0 ± 6.8
Height (cm)	178.3 ± 6.8	178.7 ± 6.0†	175.4 ± 7.4	176.3 ± 7.3	176.1 ± 6.9	175.1 ± 6.4	174.6 ± 7.0	178.8 ± 5.3†
Weight (kg)	80.8 ± 9.8	84.0 ± 12.6	77.8 ± 9.3§	80.8 ± 12.1†	77.5 ± 9.9	82.9 ± 14.1†	82.2 ± 11.7†	85.8 ± 12.3†
Relative weight (%)	101 ± 10	104 ± 13	100 ± 10†	103 ± 14†	99 ± 11†	107 ± 19	106 ± 15	107 ± 13†
Family history								
Sudden cardiac death	12%	22%	24%	20%	21%	32%	21%	20%
Heart attack	36%	37%	49%	52%	49%	62%	40%	30%
Heart failure†	5%	5%	6%	9%	9%	15%	7%	5%
Hypertension	26%	46%	15%	17%	17%	45%	31%	15%
Stroke‡	23%	30%	21%	19%	17%	29%	30%	15%
Risk factors								
Age ≥ 50 years	27%	50%	48%	52%	57%	59%	61%	65%
Diabetes	0.5%	5%	6%	5%	3%	12%	12%	15%
Cholesterol ≥ 250 mg/100 ml	8%	24%	21%	26%	22%	32%	30%	5%
Smoking	17%	23%	22%	35%	33%	25%	30%	15%
Blood pressure								
Systolic ≥ 160 mm Hg	1.6%	14%	1%	4%	2%	17%	16%	10%
Diastolic ≥ 95 mm Hg	4%	35%	6%	8%	3%	36%	35%	25%
Relative weight ≥ 115%	8%	17%	7%	12%	6%	33%	4%	0%
Sedentary activity status	59%	62%	54%	65%	64%	69%	72%	60%
Combinations of risk factors	40%	70%	53%	52%	49%	64%	64%	75%
Clinical classification of heart disease								
Inapparent	100%	46%	2%	4%	0.9%	0%	1%	0%
Possible	0%	41%	3%	22%	2%	1%	20%	5%
Probable	0%	4%	11%	31%	8%	16%	39%	10%
Definite	0%	8%	75%	27%	73%	65%	26%	85%

For all means and distributions, $P < 0.001$ (in relation to means of continuous variables for healthy men and for distributions of discrete variables for all men in eight columns of clinical classifications) except where indicated either $P < 0.01$ or not significant (NS).

*Mutally exclusive categories, except that of five patients with sudden cardiac arrest and successful defibrillation, one had hypertension, two others had recovered from prior myocardial infarction, and two had no history of prior heart disease.

†Not significant.

‡$P < 0.01$.

AP = angina pectoris; Healthy = inapparent heart disease before testing and unlikely to be at risk after testing, in order to select those who most closely approximate "normal" subjects. HT = hypertensive; PMI = postmyocardial infarction.

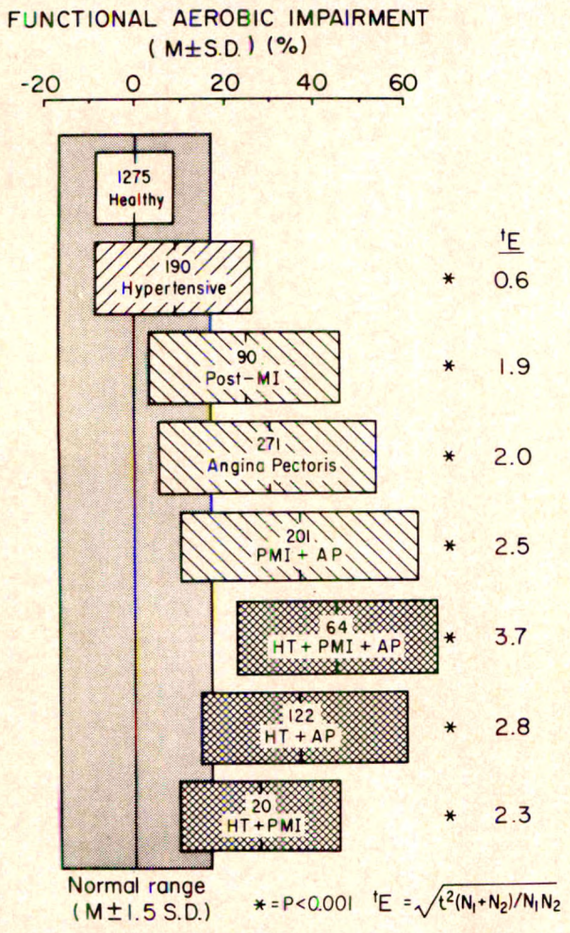

FIGURE 1. Variations in functional aerobic impairment (see text for definition) in relation to clinical classifications of men. E estimates the difference between means, relative to spread of distributions of the variable, in two populations, that is, clinical classification vs. healthy men. AP = angina pectoris; HT = hypertension; M = mean; PMI and Post-MI = postmyocardial infarction; S.D. = standard deviation. Numbers in boxes indicate number of men in each group.

patient during and immediately after testing. Use of the forms provides an extensive analytical profile of exercise performance in a brief time, and the technique can be a self-teaching method for physicians and assistants.

The degree of risk revealed by response to exercise is estimated from the largest sum of items recorded in the three columns. When the sums of normal (left) and abnormal (center and right) items are identical, the risk is arbitrarily considered "questionable."

The possible mechanisms of future cardiac events—angina or infarction from myocardial ischemia versus sudden cardiac death from arrhythmia—are also identified whenever feasible, primarily from the clinical interpretation of the electrocardiographic responses. In addition, the possibility of heart failure is predicted from subnormal circulatory responses consistent with left ventricular power failure. Similarly, evidence of a major atrioventricular conduction disorder—not as yet observed in these men—would be considered an indicator of possible development of complete atrioventricular heart block.

Because of differences in age and habitual physical activity among these men, neither duration of exercise nor the maximal oxygen uptake (which can be reasonably estimated from duration by a regression equation[8]) provided an adequate appraisal of the physiologic aerobic capacity of the individual subject. This was achieved, however, by derivation of functional aerobic impairment using the appropriate nomogram for sex and cardiovascular diagnosis.[8] Studies of other healthy middle-aged persons showed that the normal range of the means ±1.5 standard deviations was −20 to +20 percent (mean of 0 percent) (Fig. 1).

Results of computer analysis of ST_B responses (mean of 16 voltage readings from 50 to 69 msec after nadir of S), based upon averaged 100 beat samples at rest, during each work load, and for each of 5 minutes of recovery, as described previously,[9,10] are added after the clinical assessment. A separate classification table based upon clinical risk assessment (column assignment) and computer analysis (row assignment) defines the performance of each person tested, and is entered into the follow-up surveillance registry. Copies of these records are distributed to the computer center and to collaborating physicians after results of computer analysis have been obtained and checked for completeness and accuracy to ensure quality control.

Because of technical faults in individual calibration, transmission, recording or off-line processing of electrocardiographic signals, quantitative computer analysis of S–T segment responses is available for only 2,082 of the 2,332 men studied (89 percent). The variables recorded* from preliminary clinical examination, exercise testing and electrocardiographic analysis are stored on magnetic discs and tapes, using an improved comprehensive software package, "Conversational Computer Statistical System" developed by Kronmal et al.[11] The significance of differences in distributions of discrete variables is ascertained by the chi-square statistic,[12] significance between means for each continuous variable for men in the different clinical groups is appraised by using Student's unpaired t test.

Results

Clinical Findings Before Exercise Testing

Only the salient characteristics of healthy men, three groups of patients with a single clinical diagnosis, and four with various combinations of clinical diagnoses are presented in Table I.† The average age of the 1,275 healthy men was 44.5 years (standard deviation ± 7.4), whereas that of the three groups of men with a diagnosis of one cardiovascular abnormality was significantly greater (P <0.001)—50.3 years (± 8.3) for the 97 with prior myocardial infarction, 51.2 years (± 8.4) for the 306 men with angina pectoris and 49.3 years (± 8.7) for the 193 men with hypertension. Heights of most of the clinical patients were significantly lower, whereas weights were lower in patients with coronary artery disease, but higher in hypertensive‡ patients.

Distributions of mutually exclusive classifications of clinical certainty of heart disease, designated by the individual examining physician "inapparent," "possible," "probable" or "definite" on the basis of

* When observations have been missing, only the number actually recorded is shown: thus prevalence rates may be slightly underestimated.

† Other data on frequency of clinical characteristics and resting electrocardiographic abnormalities together with details of exercise responses are available on request to American Documentation Institute, 2000 P St. N.W., Washington, D.C.

‡ As classified by criteria used by the examining physicians.

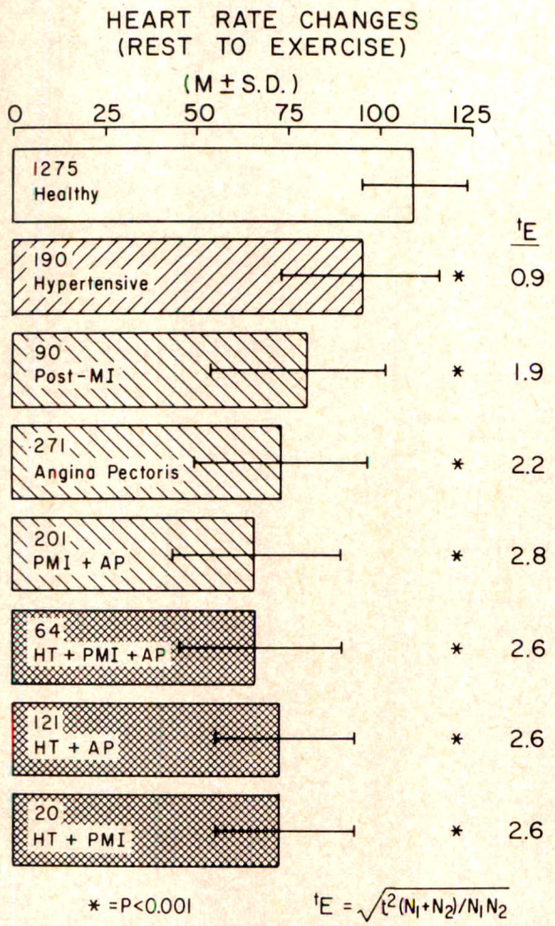

FIGURE 2. Variations in changes in heart rate from rest to maximal exercise as indexes of chronotropic reserve. Variations in N in subgroups reflect missing data in a few instances. Abbreviations as in Figure 1.

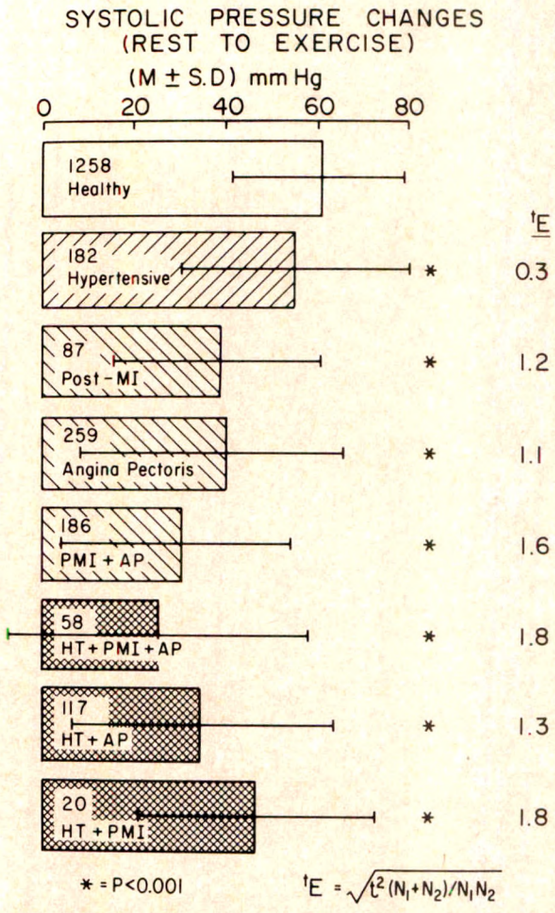

FIGURE 3. Variations in changes in systolic pressure, from rest to exercise, as indexes of inotropic reserves. Abbreviations as in Figure 1.

the history, physical examination, resting electrocardiogram and risk factors, are also shown in Table I. By definition and selection, all healthy men were classified as having "inapparent" heart disease;* 46 percent of the patients with "hypertension" and fewer than 5 percent with prior myocardial infarction or with angina were so classified. Whereas 41 percent of the hypertensive men were considered to have "possible" heart disease, no more than 25 percent in the two categories of patients with coronary heart disease were similarly classified. Conversely, the frequency of "probable" disease was less than 5 percent in the hypertensive patients and much greater in the groups with coronary heart disease. Fewer than 10 percent of the hypertensive subjects, about 33 percent of patients with angina, and 80 percent of those with prior myocardial infarction were considered to have "definite" heart disease before testing. Statistically, these distributions were extremely significant ($\chi^2 = 2802$, 21 d.f.).

Resting pressure of the healthy men averaged 123 ± 13 mm Hg systolic (standard deviation) and 77 ± 10 mm Hg diastolic. Since corresponding values for hypertensive subjects were significantly ($P < 0.001$) but only moderately higher—141 ± 16 and 90 ± 11 mm Hg, respectively—many either had "mild" hypertension or were receiving effective medical treatment. Resting pressures, particularly diastolic, in the patients with angina were very slightly greater than those of the healthy men. At rest, the patients with hypertension, recent myocardial infarction and angina had a modest prevalence of either supraventricular or ventricular premature beats.

Clinical, Circulatory and Electrocardiographic Responses to Maximal Exercise Testing

The predominant limiting symptoms at maximal exercise in healthy men were pronounced weakness of the legs (71 percent) and fatigue (25 percent).*

* Use of the term "inapparent" recognizes that if some of the men were to die of accidental or other causes, autopsy might reveal minor to moderate coronary vascular lesions although clinically they are asymptomatic, have negative findings on physical examination and exhibit no abnormalities on the resting 12 lead electrocardiogram.

* Tabulations of frequency of symptoms, signs and electrocardiographic data before exercise testing as well as during and immediately after maximal exercise are available on request to Dr. Bruce.

These symptoms were noted less frequently in hypertensive patients (50 percent) and in patients with angina (46 percent), in whom dyspnea (50 percent) and chest discomfort, tightness or pain (61 percent) were more frequent reasons for terminating exercise. Duration of maximal exertion shortened progressively with increasing evidence of cardiac disease, particularly in men with combinations of two or three diseases.

Functional aerobic impairment: The normal value derived from observed minutes of exercise in relation to age, sex and activity status, using the nomogram, was 0.6 ± 11 percent (standard deviation) (Fig. 2). The range was −16 to +17 percent, or less than that previously reported. With increasing severity of cardiovascular disease, the mean functional aerobic impairment shifted to 9 ± 19 percent, 25 ± 21 percent and 30 ± 24 percent in the patients with hypertension, prior myocardial infarction and angina, respectively (Fig. 1).

The major cardiac components of functional aerobic impairment were identified from simple measurements of circulatory and electrocardiographic responses. The chronotropic reserve of the heart, that is, the change from the resting heart rate to the highest rate observed with maximal exercise, averaged 109 ± 14 beats (standard deviation) in healthy men, 95 ± 22 in men with hypertension, 80 ± 22 in men with previous myocardial infarction, and 73 ± 24 in men with angina (Fig. 2). Similarly, an index of inotropic reserve of the left ventricle was derived from the change from resting systolic pressure to the highest pressure recorded either at or immediately after (if unable to obtain it at maximal effort) maximal exercise.* The average change in systolic pressure was 62 ± 19 mm Hg in healthy men, 56 ± 24 mm Hg in hypertensive men, 38 ± 23 mm Hg in men with previous myocardial infarction, and 40 ± 26 mm Hg in men with angina (Fig. 3). Variations in systemic peripheral resistance were indicated by small but significant changes in diastolic pressure. Both healthy men and hypertensive men showed a slight reduction in mean diastolic pressure at maximal exercise compared with their pressures at rest (Table II). Hypertensive subjects, of course, had higher diastolic pressures than healthy men. In patients with either previous myocardial infarction or angina, the level of dia-

* This is an index, since the physiologic decrease in systemic vascular resistance with strenuous exercise underestimates the actual increment in pressure.

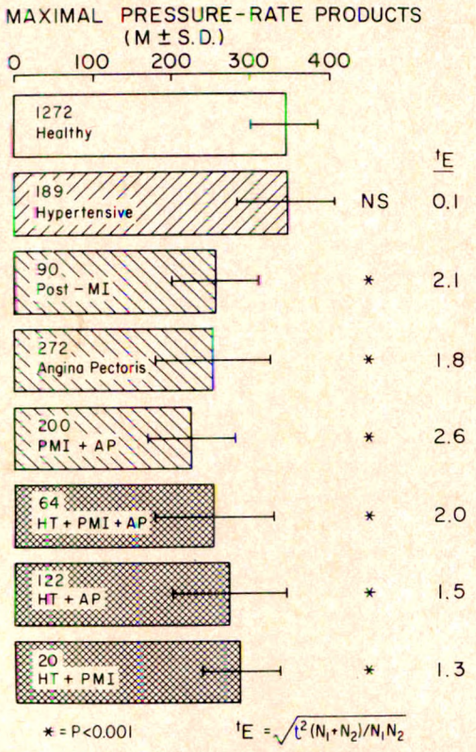

FIGURE 4. Variations in the maximal pressure-rate products as indexes of myocardial oxygen utilization. Abbreviations as in Figure 1.

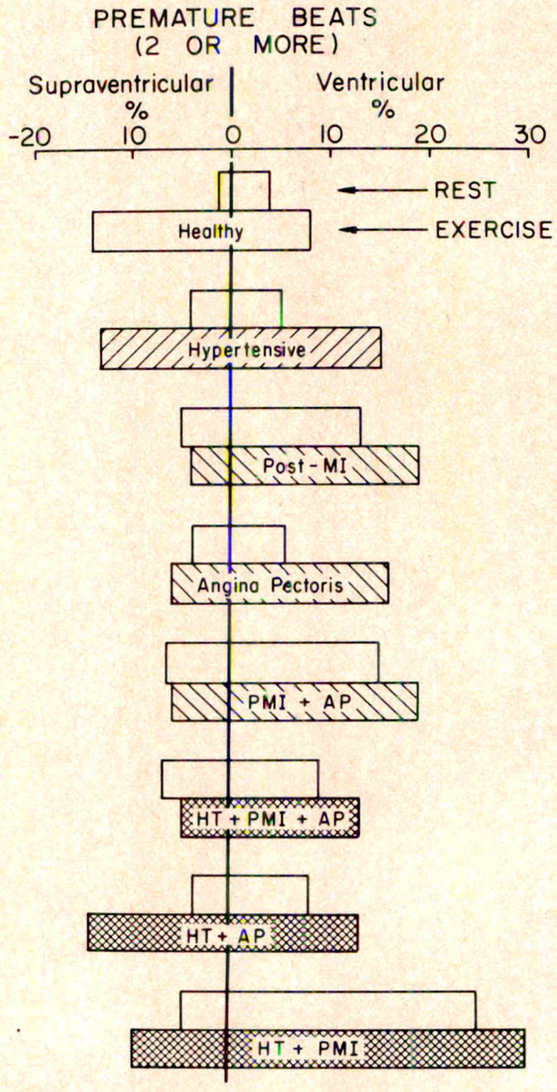

FIGURE 5. Variations in the frequencies of two or more premature beats, as indexes of arrhythmia with maximal exercise, compared with those at rest. Abbreviations as in Figure 1.

stolic pressure at rest was slightly elevated and rose with maximal exertion, indicating further arterial vasoconstriction to compensate for inadequate cardiac output.[13]

Possible differences in aerobic metabolism of the myocardium in these groups were appraised from the pressure-rate product, which is an index of myocardial oxygen uptake.[14] (Systolic rather than mean systemic arterial pressure was used, but since normal standards were obtained by the same methods, the effects of cardiovascular disease could be appraised.) Healthy men and hypertensive men had maximal values for pressure-rate product/100 of 343 ± 43 (standard deviation) and 346 ± 61, respectively (Fig. 4). Corresponding values in men with previous myocardial infarction and angina were significantly lower: 255 ± 58 and 252 ± 71, presumably because of the restrictive effects of coronary vascular disease on oxygen supply.

Arrhythmia and S–T segment displacement: Other mechanisms of cardiac impairment are revealed by arrhythmia or S–T segment displacement in the precordial electrocardiogram. All groups, including the healthy men, showed an increase in either supraventricular or ventricular premature beats (two or more) with maximal exercise (Fig. 5); the greatest number of these beats was exhibited by the hypertensive patients. More than a fourth of the healthy men (28.3 percent) had S–T segment depression of 1 mm or more (Fig. 6) for at least 60 msec of the S–T segment in the initial recovery period (by clinical interpretation), but in three fifths of these the depression was "upsloping" into the prominent upright T wave (59 percent) rather than "horizontal" or "down-

TABLE II

Functional and Circulatory Responses to Maximal Exercise and Assessment of Risk for Future Cardiac Events

	Healthy	HT	PMI	AP	PMI & AP	PMI & AP & HT	HT & AP	HT & PMI
Duration (sec)	634 ± 93	538 ± 143	444 ± 144	380 ± 162	334 ± 161	291 ± 139	331 ± 156	394 ± 119
FAI (%)	0.6 ± 11	8.5 ± 19	24.5 ± 21	30.3 ± 24	36.9 ± 26	44.9 ± 22	36.6 ± 23	27.6 ± 18
Est. $\dot{V}O_{2max}$ (ml/kg per min)	35.3 ± 5.2	30.2 ± 8.0	24.9 ± 8.1	21.3 ± 9.1	18.8 ± 9.0	16.3 ± 7.8	18.6 ± 8.7	22.2 ± 6.7
Heart Rate beats/min								
Rest	72 ± 11	77 ± 15	76 ± 13*	75 ± 12	78 ± 13	80 ± 16	79 ± 14	81 ± 14*
Stage I	108 ± 14	115 ± 18	115 ± 16	116 ± 18	120 ± 19	126 ± 19	123 ± 18	118 ± 14*
Maximal	168 ± 15	167 ± 17†	150 ± 21	144 ± 24	142 ± 23	144 ± 20	145 ± 23	148 ± 15
Rest-maximal change	109 ± 14	95 ± 22	80 ± 22	73 ± 24	66 ± 23	66 ± 23	70 ± 23	73 ± 18
% MHR								
Rest	39 ± 6	45 ± 10	49 ± 10	51 ± 10	55 ± 11	55 ± 11	54 ± 11	52 ± 10
Stage I	59 ± 7	67 ± 12†	74 ± 12	79 ± 15	83 ± 13	86 ± 14	83 ± 14	77 ± 10
Systolic BP (mmHg)								
Rest	123 ± 13	141 ± 16	121 ± 12†	125 ± 17†	120 ± 16†	143 ± 23	141 ± 19	136 ± 20
Stage I	155 ± 21	173 ± 25	143 ± 21	151 ± 25	142 ± 25	160 ± 31†	167 ± 28	166 ± 20†
Maximal	185 ± 22	197 ± 28	159 ± 26	164 ± 30	150 ± 27	168 ± 34	176 ± 33	182 ± 28
Rest-maximal change	62 ± 19	56 ± 24	38 ± 23	40 ± 26	29 ± 25	25 ± 33	35 ± 29	46 ± 26
Diastolic BP (mmHg)								
Rest	77 ± 10	90 ± 11	79 ± 8†	80 ± 10	77 ± 10†	91 ± 12	90 ± 12	90 ± 11
Stage I	76 ± 11	90 ± 13	80 ± 10	82 ± 12	81 ± 12	94 ± 14	92 ± 13	93 ± 12
Maximal	71 ± 17	88 ± 15	81 ± 13	82 ± 16	82 ± 12	93 ± 13	92 ± 14	94 ± 14
Maximal PRP/100	343 ± 43	346 ± 61†	255 ± 56	252 ± 71	221 ± 59	251 ± 77	271 ± 72	285 ± 48
Computer analysis								
Resting ST (μV) segment	51 ± 69	21 ± 81	10 ± 92	17 ± 66	12 ± 72	−27 ± 10.7	−4 ± 69	−61 ± 205
Exercise ST segment (μv/beat)	−2.1 ± 1.1	−2.1 ± 1.4	−2.2 ± 2.2	−3.1 ± 2.4	−2.5 ± 2.6*	−2.5 ± 3.5†	−2.6 ± 2.2	−2.4 ± 2.4
Recovery								
Initial (μv)	−37 ± 81	−57 ± 99*	−99 ± 163	−110 ± 137	−81 ± 155	−147 ± 245	−106 ± 118	−109 ± 105*
1 min (μv)	11 ± 69	−18 ± 98	−48 ± 141	−71 ± 110	−56 ± 133	−119 ± 240	−76 ± 108	−89 ± 92
5 min (μv)	−18 ± 55	−43 ± 86	−55 ± 108	−50 ± 68	−52 ± 105	−118 ± 228	−75 ± 82	−95 ± 150
Mean (μv)	−9 ± 58	−37 ± 88	−59 ± 117	−69 ± 86	−59 ± 110	−129 ± 234	−85 ± 92	−91 ± 76
Ischemic index‡	0.8 ± 1.4	1.3 ± 1.9	1.9 ± 2.0	2.2 ± 2.2	2.0 ± 2.1	2.8 ± 2.3	2.5 ± 2.3	3.0 ± 1.6
Risk assessment								
Unlikely	100%	87%	51%	41%	27%	21%	38%	65%
Questionable	0%	4%	12%	13%	18%	19%	15%	10%
Likely	0%	9%	37%	46%	55%	60%	47%	25%

For all means and distributions, $P < 0.001$ except where indicated $P < 0.01$ or not significant [NS].

*$P < 0.01$.

†Not significant.

‡Sum of abnormalities (maximum 6) of computer S–T segment analysis occurring at rest, during exercise and during recovery.

AP = angina pectoris; BP = blood pressure; FAI = functional aerobic impairment; HT = hypertensive; maximal PRP/100 = maximal pressure × rate product/100; MHR = maximal heart rate; PMI = postmyocardial infarction; $\dot{V}O_{2max}$ = maximal oxygen intake.

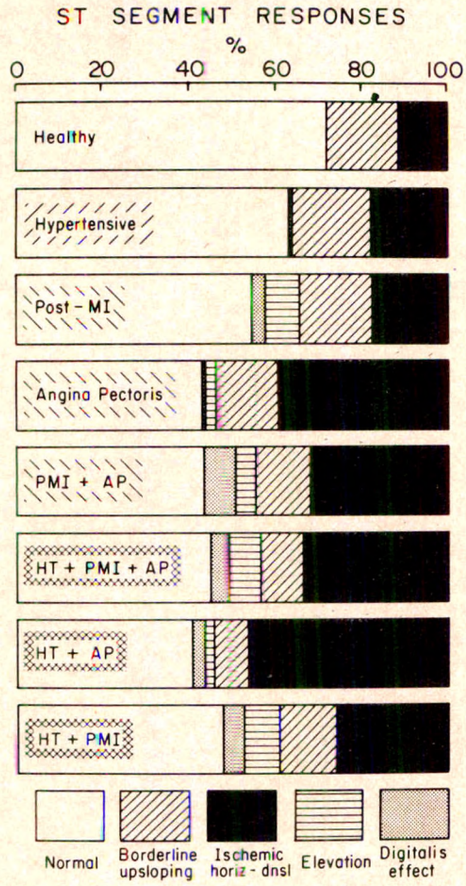

FIGURE 6. Variations in frequencies of S–T segment displacements (by clinical interpretation) as indexes of myocardial ischemia or other effects after maximal exercise. dnsl = downsloping; horiz = horizontal; other abbreviations as in Figure 1.

sloping" into a low or inverted T wave, the pattern usually considered by others to characterize an abnormal "ischemic" response to submaximal exercise. The majority of the hypertensive men showed these responses in a similar proportion of "upsloping" and "horizontal or downsloping" patterns. Patients with prior myocardial infarction or angina had a greater frequency of S–T segment deviation (43 and 63 percent, respectively), and more of these patients, especially those with angina, had horizontal or downsloping S–T segment depression. These changes were often evolutionary and persistent for a few minutes of recovery. Treatment with digoxin caused an accentuated S–T segment depression in very few of the patients with angina or prior infarction.

Only about 2 percent of all patients with cardiovascular disease and 0.5 percent of the healthy men exhibited S–T segment elevation with exercise (Fig. 6). In other studies S–T segment elevation was frequently associated with significantly larger left ventricular end-diastolic and end-systolic volumes, greater end-diastolic pressure and lower ejection fraction at rest.[15] About 40 percent of the patients with angina showed a "false negative" response, that is, S–T segment depression of less than 1 mm after maximal exercise. Computer analysis and display against heart rate showed abnormal hysteresis pathways during recovery as noted in previous studies.[4]

Of the 1,315 men apparently healthy before testing, 1,275 (97.2 percent) were classified after testing as "unlikely" and 40 (3 percent) as either "questionably" or "likely" to be at risk of future cardiac events. More than 15 percent of the hypertensive men, 49 percent of those with myocardial infarction and 59 percent of those with angina were similarly classified as "questionably" or "likely" to be at risk (Table II). Most of the risk assessment items were obtained from the clinical symptoms, signs and circulatory responses; the electrocardiographic items were of major importance in suggesting the possible mechanisms of future events, that is, angina or infarction from ischemia versus sudden cardiac death from arrhythmia.

Relation of Maximal Exercise to Target Heart Rates and Motivation

Since the type and protocol for multistage exercise testing are identical to those adopted by Sheffield,[16] it is of interest to ascertain the relation of maximal exercise, as the end point of exercise testing, to the age- and activity-adjusted target heart rates used by others. Less than 15 percent of the men in our study attained the prescribed heart rate (Fig. 7). From 3.7 percent active to 15.3 percent sedentary healthy men and from 44.7 percent active to 70.7 percent sedentary patients with cardiovascular disease could not attain the prescribed target heart rates advocated by Sheffield. Of greater interest, from 70.7 percent of sedentary to 94.2 percent of active healthy men, and 23.9 percent of sedentary to 54.3 percent of active patients with cardiovascular disease exceeded these arbitrary empirical limits.

When reexamined in relation to motivation, only 35 men (1.6 percent) were coded by the testing physicians as poorly motivated to perform exercise. Regardless of motivation, from 0 to 11 percent precisely attained the prescribed target heart rates. Whereas 14.2 percent active and 38.3 percent sedentary but well motivated men could not attain these limits, 36.4 percent of active and 12.5 percent of sedentary but poorly motivated men actually exceeded them. These observations indicate the unreliability of target heart rates in assessing functional capacity, either in health or in cardiovascular disease, and the importance of classifying habitual physical activity status when evaluating cardiovascular function.

Relation of Computer Analysis to Clinical Interpretation of S–T Segment Depression

In 1,636 tests (70.2 percent) satisfactory computer analyses of 100 beat electrocardiographic samples were available for comparison with clinical interpretation (by various physicians) of S–T segment depression in the initial recovery period after exercise. When the rigid conventional criterion of 1 mm horizontal or downsloping segmental depression for 0.1 mv or more was considered the diagnostic clinical criterion and computed ST_B voltages exceeded normal tolerance limits for two or more periods of observation, agreement was 85 percent, with only 10.8 per-

cent false positive and 4.1 percent false negative results (χ^2 = 567, 1 d.f.). When the more common upsloping segmental depression was also included, and only one computed ST_B voltage exceeded normal limits, agreement fell to 78.6 percent, with 12.8 percent false positive and 8.6 percent false negative results (χ^2 = 497, 1 d.f.).

The prevalence rate of horizontal or downsloping S–T segment depression was 16.8 percent in healthy men and only 18.9 percent in patients with prior myocardial infarction. Inclusion of upsloping depression increased the prevalence rate of S–T segment depression to 28.1 percent in healthy men and to 56.9 percent in patients with both hypertension and angina. The prevalence rates of abnormally depressed ST_B voltages by computer analysis ranged from a low of 33.7 percent in healthy men to 100 percent in the patients with hypertension and angina. In that the computer analysis provides greater frequency of abnormal responses, it is considered more reliable, because of the much larger sample for each determination and the uniform consistency in the application of rigid criteria for differentiation.

Complications of Maximal Exercise Testing

Only three types of complications were encountered; in 12 men an ataxic gait developed, and 6 men had three or more consecutive ventricular premature beats. Because both complications require stopping the test for reasons of safety, the prevalence rate of these potential hazards was only 0.8 percent. The gait disturbance was just as likely to occur in healthy men as in men with cardiovascular disease (χ^2 = 13, 7 d.f., not significant). Ventricular irritability was more likely to occur in patients with cardiovascular disease (χ^2 = 82, 7 d.f., $P < 0.001$). Only one patient had ventricular fibrillation during recovery from exercise; this hypertensive patient with angina underwent successful defibrillation and myocardial infarction did not develop. There have been no fatalities.*

Discussion

Feasibility, value and safety of study: The principles and methods of this prospective area practice study, making use of testing facilities in several hospitals, private offices, clinics and an industrial medical department, all linked by dataphones to a computer for analysis of electrocardiographic responses to maximal exercise, are workable. On the basis of the 2,332 men tested within the first 18 months and the rapid increase in the number of persons enrolled each month, the program is acceptable to patients and physicians alike.† Morbidity severe enough to require hospitalization has been only 0.1 percent, and there has been no mortality to date; thus, the procedure is safe under these circumstances when the precautionary principles and standardized protocol are followed.

The initial findings on examination and testing indicate that it is a productive study. It provides a more informative appraisal of the history of exertional symptoms and a more meaningful examination of the ambulatory patient with coronary artery disease than has heretofore been possible by noninvasive techniques. These results are due to determination of functional limits and observation of several cardiac mechanisms of impaired function.

The organization of pertinent data readily leads to further education of the supervising physicians and their assistants and provides a definable basis for risk assessment for future cardiac events. The assessment can be performed reliably, objectively and with documentation within 5 minutes, which is the usual time allowed for the patient to recover from the stress of maximal exertion. This evaluation is also compared with that of a totally independent computer analysis of the electrocardiographic responses. In addition, the study provides an opportunity to standardize criteria for evaluation and to facilitate an effective approach to quality control. Analysis of a large number of variables stored in the computer file is expedited by an advanced computer hardware/software system.

Assessment of cardiovascular function: Despite similarity of age and clinical diagnosis of the patients studied, there are highly significant functional differences in the assessed severity of cardiovascular disease, depending upon whether the patients report for examination in private offices or in teaching hospitals. Contrary to expectations of physicians unfamiliar with maximal exercise testing, few patients have been inappropriately motivated to perform.

The value of using target heart rates[16] as a uniform end point of exercise can be seriously questioned. The importance of habitual level of physical activity

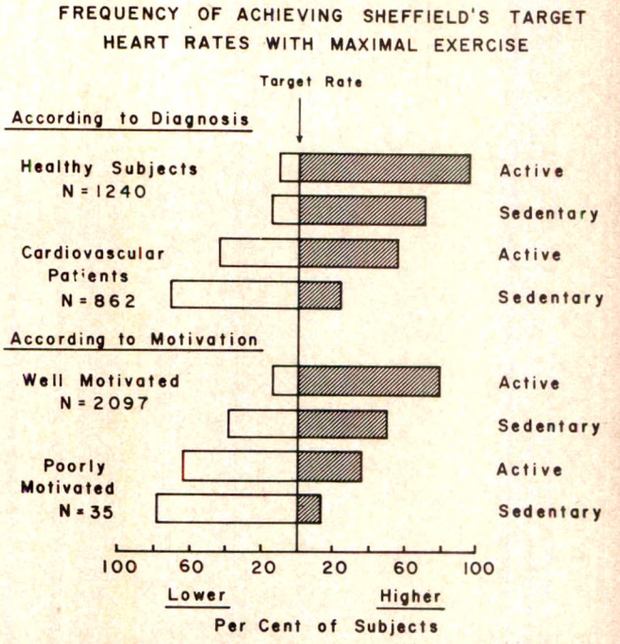

FIGURE 7. Variations in numbers of persons who either failed to attain or exceeded the age- and activity-adjusted target heart rates recommended as desirable end points for exercise testing by the same protocol as used in this laboratory for many years. See text for comments.

* Even though a few patients died suddenly during coronary arteriography or in cardiac surgery at a later date.

† One year later the enrollment had increased to 6,620 persons.

should not be disregarded in assessing cardiovascular function. Neither should it be neglected in predicting longitudinal changes with aging[18] or effect of cardiovascular disease on survival.[19]

Cardiac mechanisms of functional impairment may be appraised with respect to chronotropic and inotropic reserves of the left ventricle, index of myocardial aerobic metabolism, arrhythmias and symptomatic or unsymptomatic myocardial ischemia. Even the effects of aging on these variables may be differentiated from the effects of ischemic heart disease.[6]

Just as there are significant gradients in degree of functional aerobic impairment, there are similar gradients in the cardiovascular components of disease in a cross-sectional comparison of the clinical diagnostic classifications. For example, hypertension without apparent heart disease exerts much less restriction of cardiovascular function than either the anginal syndrome or postmyocardial infarction categories of coronary artery disease. For the few available ambulatory survivors of infarction who also exhibit manifestations of angina and hypertension, functional impairment is greater than for patients in the other six clinical categories studied. Conversely, when hypertension complicates either angina or infarction (but not both together) there is less functional impairment and postexertional myocardial ischemia. Does the greater perfusing pressure compensate, in part, for significant stenotic or occlusive lesions of the sclerotic coronary arteries, or both?

Functional effects of various types of therapeutic interventions have been reported previously in relation to the effects of medical treatment with nitroglycerin,[19] surgical treatment with saphenous vein grafting,[20] and physical training of patients with coronary artery disease.[21] Other aspects will require collection and analysis of more data to achieve adequate evaluation. These include the reproducibility of findings when there is no change in the clinical condition, as well as changes that occur with time as disease progresses in its natural history. Variations in maximal exercise performance in relation to the natural history of hypertensive disease[22] and divergent effects of antihypertensive therapy in the early phases of the natural history[23] have also been reported.

Predictive value of study: The most important question regarding validity of predictions must await the enrollment of a larger number of healthy subjects and patients with cardiovascular disease, as well as an adequate period of follow-up observation. In an earlier, pilot study on 211 healthy men followed up for 8 years, the sensitivity and predictive risk ratio of postexertional S–T segment depression were two to three times greater with this multistage test of maximal exercise than that observed in the same men with the double Master two-step test.[4] Already follow-up data on the first 1,000 men in the Seattle Heart Watch indicate that evaluation of the relative predictive value of several variables will be feasible.

Acknowledgment

We gratefully acknowledge the many who assisted in these studies.

Doctors: Hernan Alvarez, Wyman Andrus, Robert Baum, Edward Bigler, Leonard Cobb, Allen Doan, John Doces, Harold Dodge, Kenneth Eyer, Richard Foster, Gordon Hale, Karl Hammermeister, Charles Hansing, Robert Hoskins, Steve Johnson, Robin Johnston, Harold Kennedy, Donald Kestle, Robert King, Wolfgang Kluge, Eugene Lapin, Won Lee, Robert Levenson, Gordon Logan, Wayne Lowe, John Mazzarella, John McDonough, William Meade, John Murray, Manfred Niederberger, John Ormsby, John Petersen, John Peterson, Gracoma Pirzio-Biroli, Allan Pribble, Howard Pyfer, James Reed, Robert Riggins, James Ritchie, Simeon Rubenstein, Werner Samson, Floyd Short, David Silverstein, Douglas Stewart, Donald Tanner, Donald Vine, Allen Voigt and Robert Wills.

Assistants: Bessie Balch, Elean Berry, Jan Betts, Marion Chong, Elsie Bigelow, Evelyn Danner, Bud Doane, David Dora, Ellen Foley, Dick Frederick, Edith Hayes, Violet Horton, Deborah Ide, Mary Keeble, Jan Kennedy, Gaylon Kipp, Elma Kipper, Mindy Knudsen, Opal McClelland, Wendy Nelson, Kathy Oss, Barbara Pacquer, Eleanor Rhyberg, Mary Rogers, Virginia Rostad, Violet Schmidt, Janet Shaffer, Chris Swanson, Janet Tapia, Evie Tolzmann, Lorna Urbick, Shirley Witkaneck, Nora Wood, Eurydice Wooten and Evelyn Zike.

Cardiology, Biostatistics and Epidemiology staff members: Jon Barry, Robert Braunwart, Dave Carge, Nina Chinn, Haydi Curci, Jackie Eddy, Lila Groen, Verona Hofer, Bernetta Jones, Lucile Jones, Paula Kanarek, Art Marriott, Tom Marson, Gladys Pettet, Alison Ross, Sheri Schaeffer, Linda Styron, Glenn Weller and John West.

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Electrocardiogram in Acute Pericarditis

Distributions of Morphologic and Axial Changes by Stages

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Among 50 patients with uncomplicated acute pericarditis, 48 showed classic stage 1 S–T segment deviations; stage 3 T wave inversions developed in 32 patients. Electrocardiographic changes during the transitional stages 2 and 4 were recorded in 23 and 32 patients, respectively. Stage 1 orientation of the S–T segment frontal plane mean vector (ÂS–T) corresponded closely to ÂT and ÂQRS. Precordial S–T segment elevations occurred with increasing frequency from leads V_1 to V_6. Subsequent T wave inversions produced a wide dispersion of ÂT in stage 3 between −50° and +100°; precordial T waves were always inverted in leads V_5 and V_6. Forty-one patients had P–R segment shifts; in 93 percent ÂP–R was concentrated between −120° and −150°, directly opposite to ÂP. ÂS–T was oriented to the left and anterior and inferior, representing the generalized subepicardial ventricular myocarditis of acute pericarditis. ÂP–R was oriented to the right and posterior and superior, representing the corresponding generalized atrial injury. The wide dispersion of ÂT in stage 3 is consistent with inhomogeneity of the ventricular recovery process after injury.

The electrocardiogram in the majority of patients with acute pericarditis[1–3] classically evolves in a sequence of four stages[4] based on S–T and T wave changes, part or all of which can be virtually diagnostic in the absence of other evidence of pericarditis[3] (Fig. 1 and 2). The typical sequence is outlined in Table I. The ubiquitous S–T segment deviations of stage 1 and subsequent T wave inversions in stage 3 are the electrocardiographic hallmarks of acute pericarditis. Stage 2 is an unstable continuum between stages 1 and 3. In stage 4 the widespread T wave abnormalities of stage 3 undergo more or less complete restitution toward the configuration of the prepericarditis tracing. P–R segment deviations,[3] appearing in stage 1 or 2, or in both (occasionally in stage 3), are almost as characteristic as the classic S–T segment deviations[3,5,6] and are not due to changes in heart rate.[5] One or another stage may be missing depending on the frequency of electrocardiographic monitoring in relation to the tempo of the inflammatory process.[1,3]

Diagnosis of acute pericarditis by electrocardiogram alone is fairly certain if the S–T segment deviations of stage 1 are recorded (Fig. 1 and 2), whether or not those of any other stages can be documented. The generalized T wave inversions of stage 3 are highly suggestive of the diagnosis, yet are indistinguishable from various patterns representing biventricular "strain" and diffuse myocardial injury. Thus, in the absence of stage 1 S–T changes, the electrocardiogram is ancillary to other evidence in diagnosing acute pericarditis, such as identification of unmistakable pericardial friction (Fig. 3)[7] or definite evidence of an inflammatory pericardial effusion or cardiac tamponade.[8] The aim of this investigation was to characterize by lead and by vector orientation the distributions of electrocardiographic changes in patients with uncomplicated acute pericarditis and more or less classic electrocardiographic evolution.

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TABLE I

Four-Stage ("Typical") Electrocardiographic Evolution of Acute Pericarditis

Stage	Leads of "Epicardial" Derivation			Leads Reflecting "Endocardial" Potential		
	S–T Segment	T Waves	P–R Segment	S–T Segment	T Waves	P–R Segment
1	Elevated	Upright	Depressed or isoelectric	Depressed	Inverted	Elevated or isoelectric
2 Early	Isoelectric	Upright	Isoelectric or depressed	Isoelectric	Inverted	Isoelectric or elevated
Late	Isoelectric	Low to flat to inverted	Isoelectric or depressed	Isoelectric	Shallow to flat to upright	Isoelectric or elevated
3	Isoelectric	Inverted	Isoelectric	Isoelectric	Upright	Isoelectric
4	Isoelectric	Upright	Isoelectric	Isoelectric	Inverted	Isoelectric

Material and Methods

The subjects were 50 patients with clinically acute pericarditis and no evidence of heart disease. Etiologic assignment of pericarditis was as follows: "Idiopathic pericarditis" (syndrome) or "pericarditis of uncertain origin" (17 cases); associated with neoplasia (12 cases); viral, including 1 during hepatitis (10 cases); possible bacterial (2 cases); connective tissue diseases (9 cases). All patients had definite electrocardiographic changes, but the diagnosis of acute pericarditis could be made independently of the electrocardiogram. For this study acute pericarditis was considered present (irrespective of symptoms) on detection of a pericardial rub or fresh effusion, or both. Forty-four patients had a pericardial rub (Fig. 3), two had an effusion and four had both. Twelve lead electrocardiograms were analyzed for sequential S–T segment, T wave and P–R segment changes. The T–P interval was the base line for P–R and S–T segment measurements. Directional changes were noted for each lead, and frontal plane mean vectors (Â) were plotted on the hexaxial scale. Since this was a retrospective study, numerical and percentage distributions of electrocardiographic changes were considered to demonstrate significant trends rather than precise prevalence rates of particular events. It was recognized that one or more stages might be absent because of late arrival or early discharge of the patient or rapid evolution of the inflammatory process.

Results

Axial orientations are summarized in Table II in terms of percentage distributions for each change. The statistical base varied with the number of subjects demonstrating each stage as follows: Stage 1 was present in 48 patients, stage 2 in 23, stage 3 in 32 and stage 4 in 37. (Stage 2, always an unstable transitional phase of S–T and T wave changes [Table I], was analyzed for P–R segment changes only.)

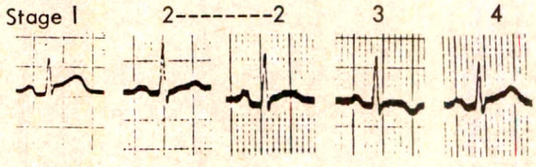

FIGURE 1. Classic four stage evolution of electrocardiogram in acute pericarditis according to S–T and T wave changes. Stage 2 is transitional with J points on the base line before T waves begin to flatten. T wave inversion characterizes stage 3. Stage 4 represents electrocardiographic resolution. Note the P–R segment depression, particularly in late stage 2 **(middle panel).**

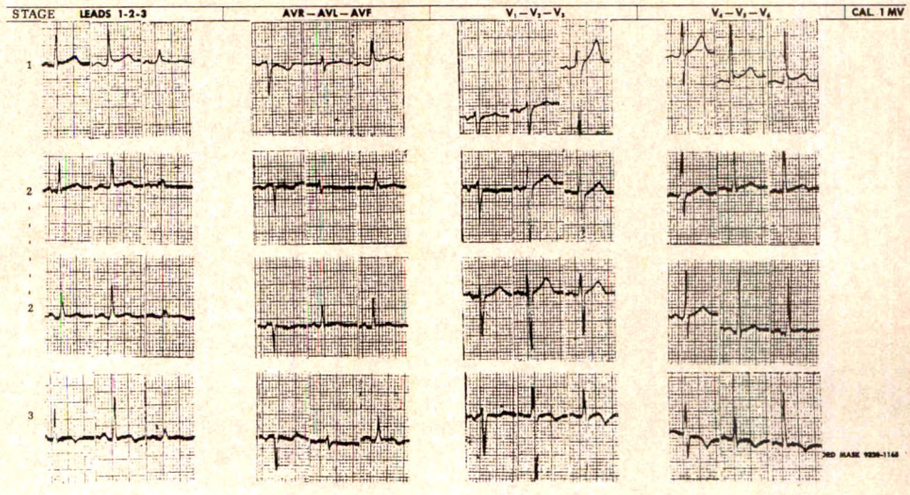

FIGURE 2. Electrocardiographic stages 1, 2 and 3 diagnostic of acute pericarditis. In stage 1, S–T segment elevation occurs in most leads of "epicardial" derivation. Note the isoelectric S–T segment in lead aVL (ÂS–T = +60°) and in leads V_1 and V_2. Late in stage 2 (third tracing from the top) P–R segment depressions occur, best seen in leads I, II, aVL, aVF and V_4 to V_6.

Heart rate: The heart rate ranged between 68 and 136 beats/min in stage 1 and between 63 and 125 beats/min in stage 2, nearly always permitting accurate delineation of waves and segments. In a single case (heart rate 136 beats/min) the proximity of the P and T waves obliterated the T–P segment so that the electrocardiogram was scored "negative" for S–T and P–R deviations.

S–T segment deviations: The numerical distribution of ÂS–T in 48 patients is shown in Figure 4. The percentage distribution (Table II) shows that 80 percent of frontal plane mean S–T vectors were oriented in the intermediate axis range lying between +30° and +60°, corresponding to 65 percent of T and 56 percent of QRS vectors. On either side of this range, horizontal (14 percent) and vertical (6 percent) ÂS–T also corresponded generally to the distributions of ÂT and ÂQRS. Precordial S–T segment deviations were seen in 47 of these 48 patients and are additionally broken down in Table III according to frontal plane QRS axis orientations. (An analysis of variance of these figures showed no trend for the distribution of precordial S–T deviations to correspond to frontal plane axes.) For the entire series, 46 of 47

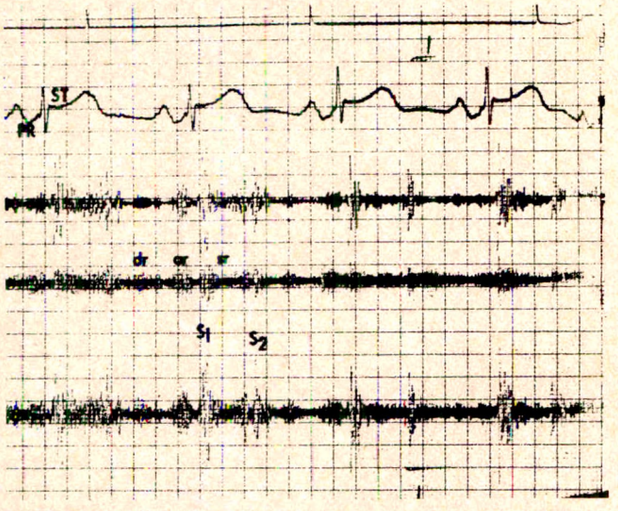

FIGURE 3. Acute pericarditis with typical three phase pericardial rub. **Top tracing:** electrocardiographic lead II showing stage 1 with simultaneous P–R segment depression and S–T segment elevation. Bottom three tracings: multifilter phonocardiogram of rub; *ar* =presystolic (atrial) component; *dr* = diastolic component; *sr* = ventricular systolic rub; S_1 and S_2 = first and second heart sounds, respectively.

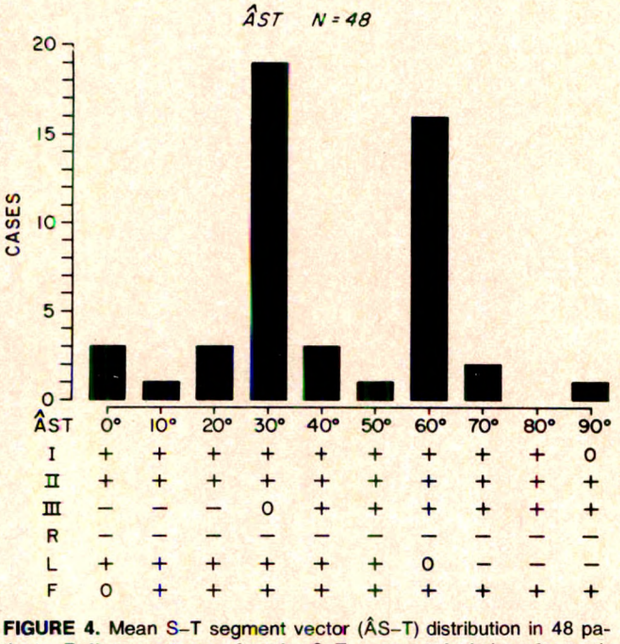

FIGURE 4. Mean S–T segment vector (ÂS–T) distribution in 48 patients. **Bottom:** patterns of scalar S–T segment deviations for each limb lead. 0 = isoelectric; + = elevated; − = depressed.

TABLE II

Mean Frontal Vector Distribution

Orientation (Degrees)	Percent of Group ÂQRS	ÂT (Stage 1)	ÂPR	ÂP	ÂST	ÂT (Stage 3)
"Right"						
+100						6
+110						0
+120						3
+130						0
+140						0
+150						3
+160						0
+170						9
+180						0
"Left"						
−170						9
−160						0
−150			38			14
−140			10			6
−130			5			17
−120			40			6
−110			0			3
−100			2			6
−90			5			3
−80						9
−70						0
−60						0
−50						6
−40						
−30	4					
"Horizontal"						
−20	2					
−10	2	2				
0	8	8		1	6	
+10	8	17			2	
+20	6	6		1	6	
+30	20	26		5	40	
"Intermediate"						
+40	8	12		20	4	
+50	10	17		43	2	
+60	18	10		25	34	
"Vertical"						
+70	8	2			4	
+80	2			5	0	
+90	4				2	

patients had S–T segment elevations in leads V_5 and V_6. In lead V_1 only 8 had S–T elevations, whereas 14 had S–T depressions, and in 25 patients the S–T segment was isoelectric.

T wave changes. In stage 1 the normal mean frontal T wave vectors were concordant with the QRS vector (Table II). In stage 3 the T wave vectors had shifted as a whole to a large range with a wide dispersion between −50° and +100°, (an arc of 210°) away from the normal stage 1 ÂT orientations (Table II and Fig. 5). There was some concentration (37 percent of cases) of T wave vectors in the sector between −130° and −150°. Precordial T wave changes generally followed the lead by lead pattern of S–T deviations shown in Table II, with T wave inversions corresponding to earlier S–T elevations. The inverted T waves increased in frequency from lead V_1 to lead V_6. In nine patients (28 percent) the T wave was inverted in all precordial leads. In all cases (100 percent) T waves became completely or partially inverted in leads V_5 and V_6. Thus, both S–T and T wave changes were most frequent in the left precordial leads.

P–R segment changes: P–R segment shifts (Fig. 1 to 3) appeared in 40 patients in stage 1 or 2, or both, and in 1 patient in stage 3 only. Table II and Figure 6 show that 38 (93 percent) of the frontal plane P–R vectors in these patients were oriented in the sector between −120° and −150°, approximately directly opposite to the corresponding P wave vectors (ÂP), 88 percent of which were in the sector between +40° and +60°. Thirty-two (80 percent) of the P–R vectors were oriented 180° ± 10° from ÂP. The P–R segment was always negative in leads aVF and II and always positive in lead aVR. In precordial leads V_2 to V_6, P–R segments were always negative (38 to 40 patients, depending on lead) or isoelectric (1 to 3 patients). In 37 patients this was also true of lead V_1, but in the remaining 4 the P–R segment in lead V_1 was elevated. It was never elevated in leads V_2 to V_6.

TABLE III

Precordial S–T Deviations According to Frontal Plane Axis Orientations (no. = 47)

	V_1	V_2	V_3	V_4	V_5	V_6
Â QRS +20° to −30° (no. = 13)						
+	3	5	9	11	11	12
0	6	8	4	3	1	1
−	4	0	0	0	0	0
Â QRS +30° to +50° (no. = 19)						
+	1	11	14	119	19	19
0	12	8	5	0	0	0
−	6	0	0	0	0	0
Â QRS +60° to +90° (no. = 15)						
+	4	8	11	12	15	15
0	7	5	4	3	0	0
−	4	2	0	0	0	0
Totals						
+	8	24	34	42	46	46
0	25	21	13	6	1	1
−	14	2	0	0	0	0

+ = S–T segment elevated; 0 = isoelectric S–T segment; − = S–T segment depression.

Discussion

Subepicardial injury vectors: Forty-eight of 50 patients showed the generalized S–T segment deviations of stage 1. (In the remaining two patients the electrocardiogram was first seen during stage 2 with return to the base line of the S–T junction and subsequent T wave changes.) The S–T vectors were oriented concordantly with the mean QRS vector in most cases (Table II), the majority being in the intermediate axis range, as would be expected in a population without heart disease. Figure 4 shows both the nu-

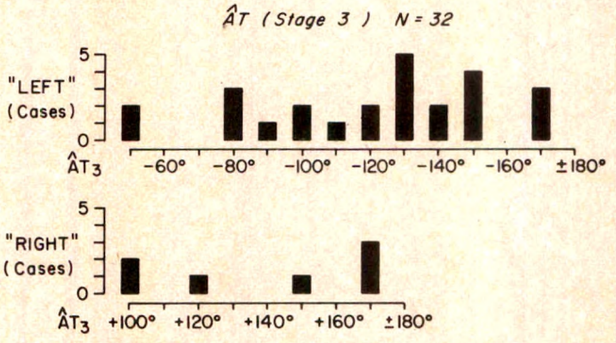

FIGURE 5. Distribution of T wave vector (ÂT) in stage 3. There is no range of predilection although most cases are oriented to the left on the hexaxial scale (see text).

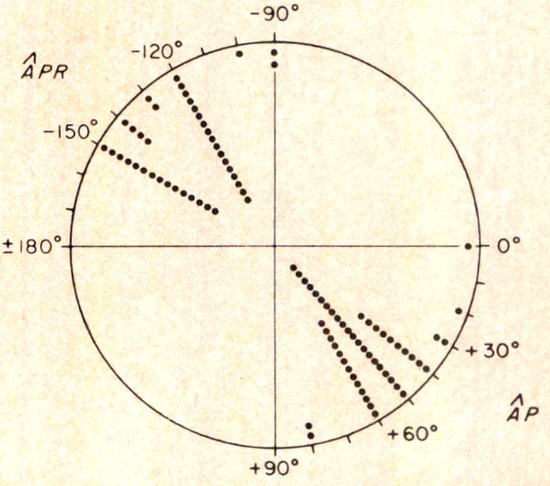

FIGURE 6. Mean frontal plane P–R segment vector orientation (ÂP–R) plotted with corresponding mean P wave vectors (ÂP) on the hexaxial scale to the nearest 10°. ÂP–R tended to be oriented to the right and superiorly and was approximately 180° opposite to ÂP, corresponding to the expected spatial orientation of atrial T wave vectors. (Although ÂP–R may be considered "left" on the hexaxial reference scale, this orientation is spatially rightward.)

merical distribution of frontal plane S–T vectors and the direction of the S–T segment deviations in each of the corresponding limb leads. Thus the S–T segment was always positive in lead II and negative in lead aVR; in lead III it was negative or positive depending on whether the QRS axis was, respectively, horizontal or vertical. The reverse was true of lead aVL. Such S–T orientations concordant with the QRS and T vectors (Table II) are consistent with a vector of generalized subepicardial injury oriented predominantly leftward and inferior in the frontal plane, that is, mainly toward the cardiac apex.[1–4] The precordial S–T segment deviations (Table III) yielded a mean horizontal plane S–T vector oriented leftward and anterior, consistent with the same concept. Thus, the net spatial ÂS–T was to the left and inferior and anterior.

In contrast to the more or less concentrated S–T vectors of acute injury, the T wave changes in stage 3 yielded a very wide range of orientation for ÂT (Fig. 5 and Table II), consistent with wider dispersion (inhomogeneity) of the ventricular repolarization process after the subepicardial injury.

Atrial injury vector: Because of the appearance of the P–R vector in more than 80 percent of the patients studied (41 of 50), P–R segment deviation must be considered almost as characteristic of acute pericarditis as the classic S–T segment shift. ÂP–R was always oriented to the right and superiorly (Fig. 6). Since no patient had P wave abnormalities, P–R segment deviations probably represent subepicardial atrial injury. ÂP–R tended to be close to 180° away from ÂP (Table II); that is, it followed the expected orientation of the atrial T wave.[9,10] Thus, the electrocardiographic registration of atrial injury in acute pericarditis is analogous to that of the stage 1 ventricular subepicardial injury in that each follows the orientation of its respective normal recovery (T) wave. Since most atrial tissue lies posteriorly, to the right, and relatively cephalad of the ventricles, the orientation of a vector of generalized atrial injury (ÂP–R) would be expected to be to the right and superior (as shown by the frontal plane ÂP) and also posterior. The predominant P–R segment depressions across the precordium document the posterior component. Because of these P–R segment deviations, it is of practical importance in acute pericarditis to consider the T–P segment to be the electrocardiographic base line to avoid mistaking P–R segment depression for S–T segment elevation.

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Posterior Wall Velocity: An Unreliable Index of Total Left Ventricular Performance in Patients with Coronary Artery Disease

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Posterior wall velocity determined by use of echocardiography has been proposed as an index of total left ventricular performance in patients with ischemic heart disease. Accordingly, in 9 normal subjects and 39 patients with angiographically documented coronary artery disease, we compared mean endocardial posterior wall velocity determined by echocardiography with echocardiographic and biplane cineangiographic calculations of ejection fraction and the mean rate of circumferential fiber shortening (mean V_{CF}), and with externally recorded systolic time intervals. All studies were performed on the same day in each patient. Mean endocardial posterior wall velocity averaged 4.6 cm/sec (range 2.9 to 8.7) and correlated poorly with echocardiographic ejection fraction ($r = 0.47$), cineangiographic ejection fraction ($r = 0.26$), cineangiographic mean V_{CF} ($r = 0.47$), the ratio of preejection period to left ventricular ejection time ($r = -0.35$) and the preejection period corrected for heart rate ($r = -0.30$). Substitution of maximal for mean endocardial posterior wall velocity did not improve the separation of normal from depressed left ventricular performance. Epicardial posterior wall velocity, a measurement more easily obtainable than endocardial posterior wall velocity, also did not correlate well with systolic time intervals or with ejection fraction or mean V_{CF} derived from the echocardiogram and cineangiogram. Both endocardial and epicardial posterior wall velocity values were poorly reproducible on a day to day or a beat to beat basis. We conclude that neither endocardial nor epicardial posterior wall velocity, whether derived as a mean or a maximum, provides an accurate measure of total left ventricular performance in patients with coronary artery disease.

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There has been considerable recent interest in the noninvasive estimation of left ventricular performance in man. Both echocardiography[1–4] and externally recorded systolic time intervals[5] have been proposed as methods suitable for serial atraumatic assessment of myocardial function. It has been suggested that echocardiographic measurement of left ventricular posterior wall velocity might provide a simple reproducible method for serial evaluation of total cardiac performance.[6–8] Accordingly, we compared echocardiographic estimates of posterior wall velocity with other echocardiographic indexes of left ventricular function and with externally recorded systolic time intervals and indexes of myocardial performance derived from cineangiocardiograms in patients with and without coronary artery disease.

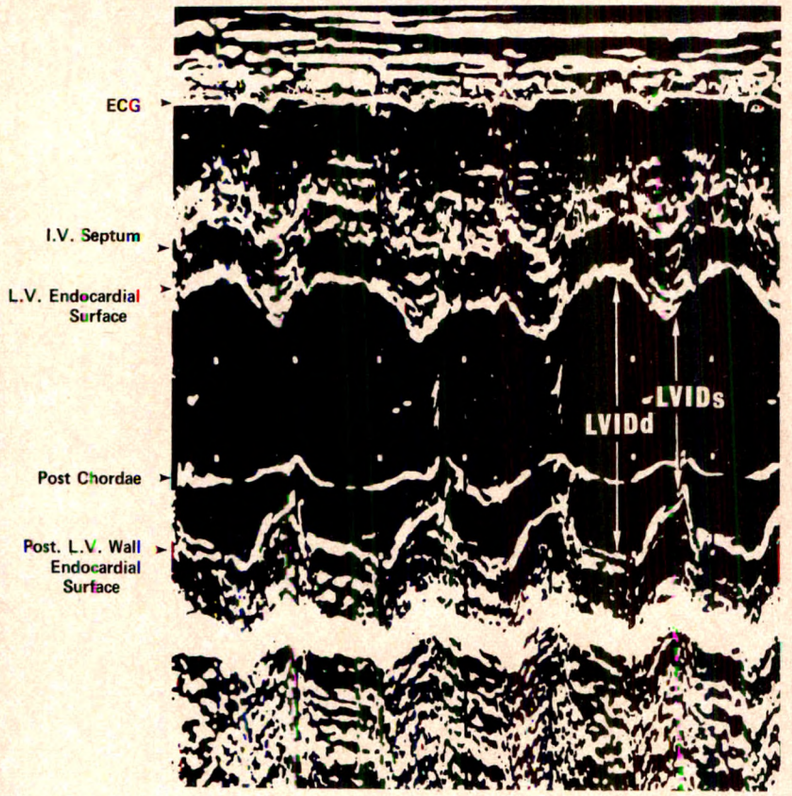

FIGURE 1. Echocardiogram showing the left ventricular (L.V.) endocardial surface of the interventricular (I.V.) septum and the left ventricular posterior (post.) wall endocardium. Careful visualization of the posterior chordae insured both accurate definition of the left ventricular endocardium and consistent localization of the ultrasound beam. Automatically incorporated into the display are the simultaneous electrocardiogram and time-distance markers. Distance is plotted on the ordinate and time on the abscissa. The left ventricular internal end-diastolic dimension (LVIDd) between endocardial surfaces was measured along a vertical line drawn through the QRS complex. The left ventricular internal end-systolic dimension (LVIDs) was defined as the smallest distance separating the endocardial surfaces of the septum and the left ventricular posterior wall. Ejection time (ET) was taken as the length of time from the peak of the QRS complex to the maximal excursion of the left ventricular posterior wall, less 50 msec for the preejection period when no appreciable fiber shortening occurs.[11,12] In each instance, posterior wall velocity was derived from the same cycles used to calculate ejection fraction and mean V_{CF}. In the case illustrated, a sinus arrhythmia was present.

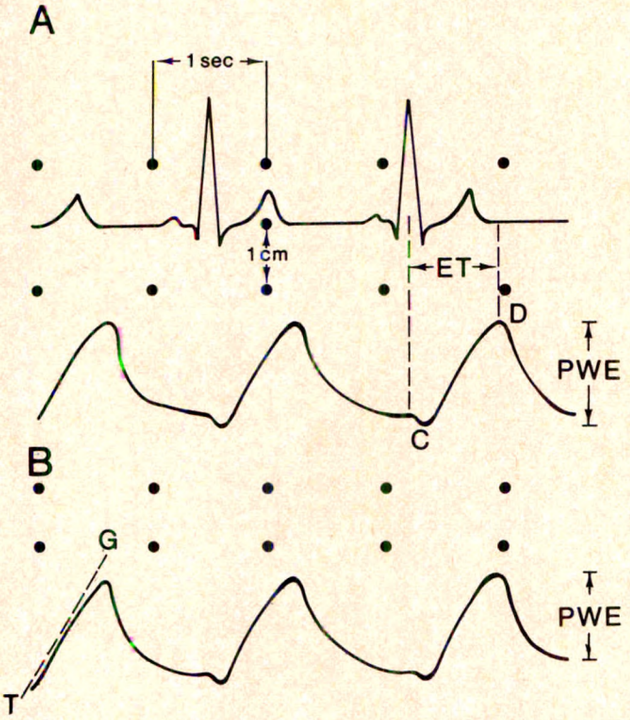

FIGURE 2. Two methods for calculating left ventricular posterior wall velocity are shown. **A,** the mean posterior wall velocity is equal to posterior wall excursion (PWE) measured from points C to D, divided by the ejection time (ET), as defined. **B,** maximal posterior wall velocity is calculated by constructing a tangent (TG) to the steepest part of the left ventricular posterior wall and expressing the slope in centimeters per second.

Methods

In 48 patients admitted for diagnostic cardiac catheterization and coronary angiography, echocardiographic estimates of posterior wall velocity and left ventricular dimensions were performed by one observer within 24 hours of catheterization. Thirty-nine of these patients had coronary artery disease; the remaining nine had no evident cardiac disease. Ten additional patients were studied daily by echocardiography for an average of 6 days in the coronary care unit; seven of these patients had documented acute myocardial infarction, and the other three had angina pectoris without overt infarction. Another nine normal subjects were also examined daily by echocardiography for an average of 3 days. All echocardiographic studies were performed with subjects in the basal fasting state, in either the supine or left lateral decubitus position.

Methods of ultrasound echocardiography have previously been described in detail.[3,9,10] A commercially available ultrasonoscope (Ekoline 20, Mark II, Smith-Kline) was used with a 2.25 megaHerz, 0.75 inch transducer that had a repetition rate of 1,000 impulses/sec. Polaroid photographs of the "time-motion" echocardiographic display were made directly from the oscilloscope (Fig. 1). Careful visualization of the "x" line representing echoes from the supporting apparatus of the mitral valve ensured both accurate definition of the left ventricular endocardium and consistent localization of the ultrasound beam. In all 48 patients a complete echocardiographic left ventricular dimensional analysis was performed using methods previously described for determination of end-diastolic and end-systolic volumes and ejection fraction, mean velocity of circumferential fiber shortening, and posterior wall velocity.[3] For the latter measure, two types of determinations were made. A mean value

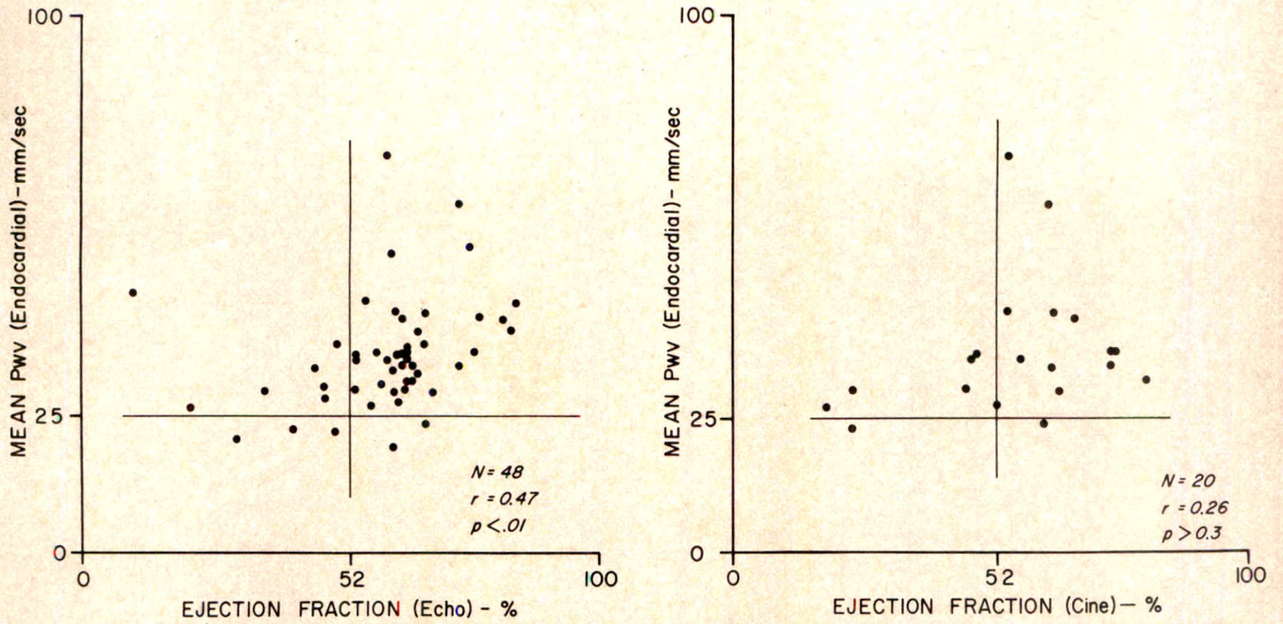

FIGURE 3. Mean endocardial posterior wall velocity (PWV) determined by echocardiography plotted against ejection fraction determined by echocardiography **(left)** and cineangiography **(right).** The **crossed lines** represent the lower limits of normal for each measurement (25 mm/sec for mean posterior wall velocity and 0.52 for ejection fraction).

for posterior wall velocity (mean PWV [cm/sec]) was calculated from the value for posterior wall excursion divided by the ejection time (less 50 msec for isovolumetric contraction, when little significant fiber shortening occurs[11] [Fig. 2]). Mean posterior wall velocity was derived at both the endocardial and epicardial surfaces. To validate the method of calculating ejection time, we compared our technique with the alternative method of measuring the duration of systole directly from the echocardiogram. For 40 of the 48 patients the correlation between results of the two techniques was excellent ($r = 0.987$, $P < 10^{-6}$). The average difference between the two determinations was 6.3 msec (range 0 to 15 msec). Neither method yielded a value consistently larger or smaller than that of the other. In the remaining eight patients, the ejection time could not be accurately determined directly from the ultrasound recording because of the initial slurring of the upstroke associated with isovolumetric systole. The left ventricular ejection time derived from the externally recorded carotid pulse tracing averaged 260.5 ± 5.0 (standard error) msec (range 178 to 338), and that obtained by the ultrasound method described averaged 259 ± 4.8 msec (range 170 to 340). There was a highly significant correlation between the two measures ($r = 0.870$, $P < 10^{-6}$). As with the previous comparison, neither method yielded a value consistently larger or smaller than that of the other.

Maximal posterior wall velocity (PWVmax [cm/sec]), calculated at both the endocardial and the epicardial surfaces, was determined from the slope of a tangent drawn to the steepest position of the anterior movement of the posterior wall echo (Fig. 2). For each determination of ejection fraction, mean velocity of basal circumferential fiber shortening (mean V_{CF}) and posterior wall velocity, five satisfactorily recorded beats were averaged. Thus, the beats from which the echocardiographic ejection fraction and mean V_{CF} were derived were from the same cycles used to calculate posterior wall velocity, thereby eliminating any bias in the comparisons among these determinations.

In the 10 patients who were studied in the coronary care unit, echocardiographic recordings were made of epicardial posterior wall movement only, since we sought to test the validity and reproducibility of the epicardial posterior wall velocity alone as an index of left ventricular performance. Recordings of the epicardial surface, which can be obtained rapidly and with minimal discomfort to the patient, were thought to be most suited to patients with documented or suspected acute myocardial infarction.

Cardiac catheterization was performed with patients in the fasting state after premedication with 100 mg of sodium pentobarbital. Left ventricular catheterization was performed by the retrograde arterial technique, and left ventricular cineangiograms were recorded at 75 frames/sec after intraventricular injection of 40 to 50 ml of 75 percent Hypaque® over 2 to 3 seconds. End-systolic and end-diastolic left ventricular volumes were estimated using the area-length method for biplane ventriculograms,[13] and the ejection fraction was calculated from these measurements.[14] Mean V_{CF} was derived from the lateral projection of the left ventriculogram by calculating the shortening of a chord drawn perpendicular to the long axis of the ventricle at one third of the distance from the midpoint of the mitral valve plane to the cardiac apex.[3,12] This chord was selected for comparison since it corresponds most closely to the plane of the ultrasound beam.[3]

Systolic time intervals were measured from simultaneous recordings of a high frequency phonocardiogram, indirect carotid arterial pulse and electrocardiogram on a multichannel recorder (Elena-Schonander Minograf) at a paper speed of 100 mm/sec, immediately after the echocardiogram. Calculations of mean intervals were derived from measurements of 10 optimally recorded cardiac cycles. Observed intervals were corrected for heart rate and sex according to the regression equations of Weissler and coworkers,[5] and expressed as indexes. The ratio of preejection period (PEP) to left ventricular ejection time (LVET) was obtained by dividing the observed PEP by the uncor-

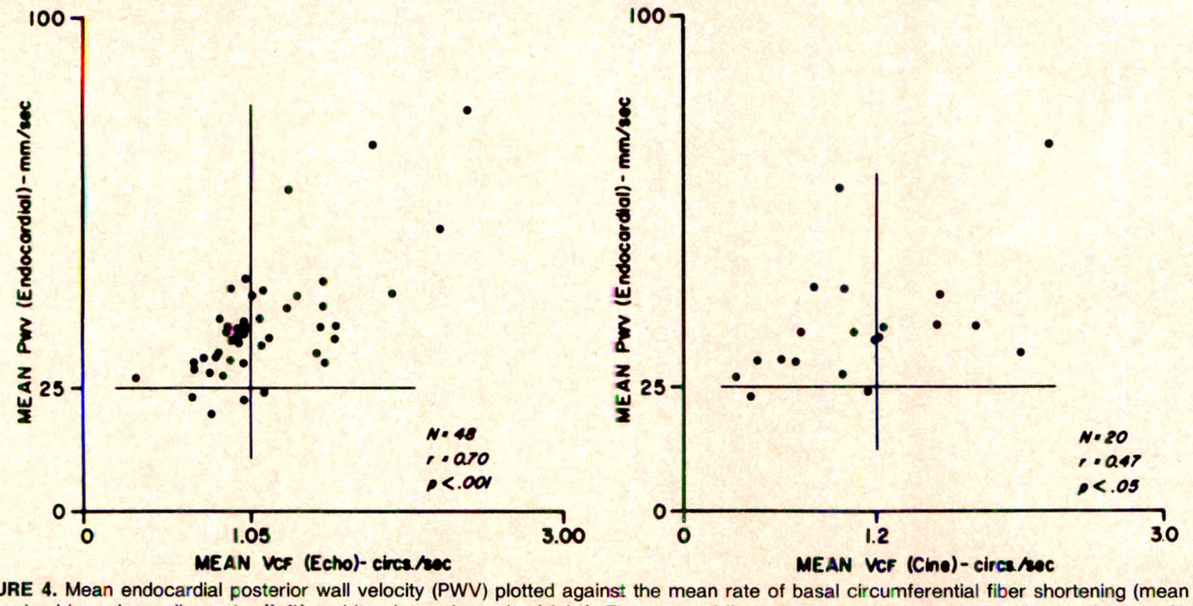

FIGURE 4. Mean endocardial posterior wall velocity (PWV) plotted against the mean rate of basal circumferential fiber shortening (mean V_{CF}) determined by echocardiography **(left)** and by cineangiography **(right).** The **crossed lines** represent the lower limits of normal for each measurement (25 mm/sec for mean posterior wall velocity, 1.05 circumferences/sec for mean V_{CF} by echocardiography and 1.20 circumferences/sec for mean V_{CF} by cineangiography).

rected LVET, since it has previously been shown that this ratio is independent of heart rate.[15]

Echocardiograms satisfactory for volume estimation and for calculation of posterior wall velocity were obtained in all 48 patients studied in the catheterization laboratory. In 20 of these patients left ventricular cineangiograms were suitable for volume and mean V_{CF} determinations; that is, there was adequate opacification of normally conducted beats that did not follow one or more premature contractions. The 10 patients studied in the coronary care unit and the 9 normal control subjects also had satisfactory echocardiograms for analysis of posterior wall velocity.

In 6 patients 16 echocardiographic dimensional analyses and determinations of systolic time intervals were performed to test observer and technique reproducibility. The average variation for echocardiographic determinations in

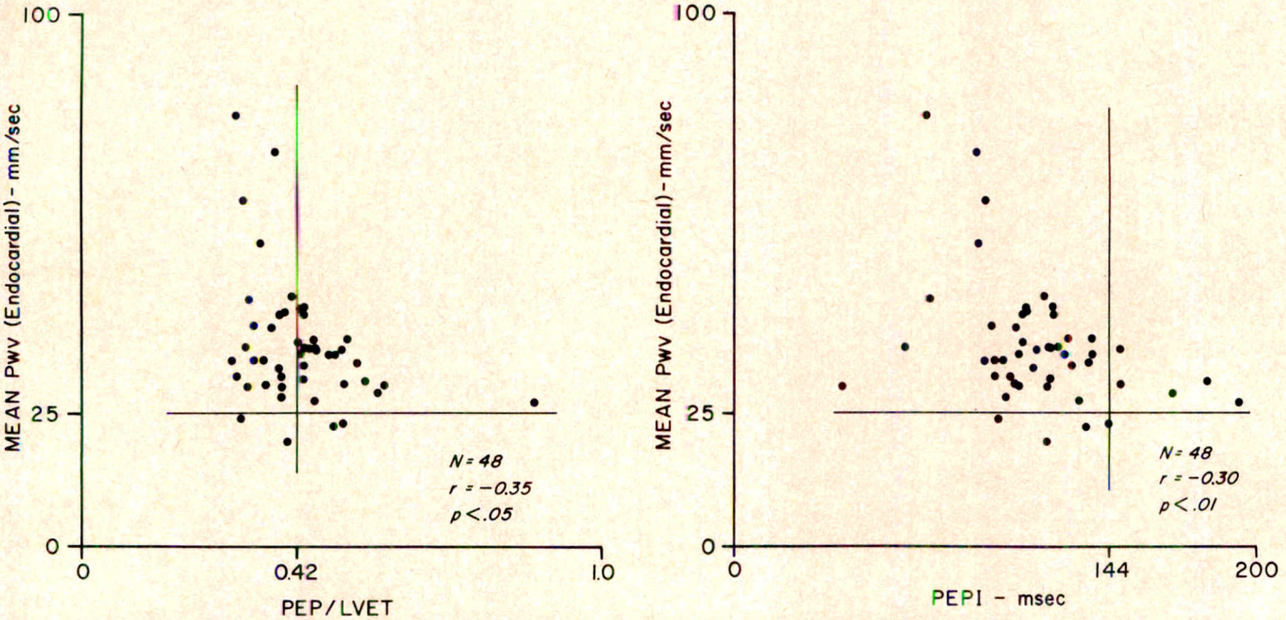

FIGURE 5. Mean endocardial posterior wall velocity (PWV) plotted against the ratio of the preejection period to the left ventricular ejection time (PEP/LVET) **(left),** and against the preejection period (PEP) corrected for heart rate (PEPI) **(right).** The **crossed lines** depict the lower limit of normal for posterior wall velocity (25 mm/sec), and the upper limit of normal for PEP/LVET (0.420) and for preejection period corrected for heart rate (144 msec).

the same patient was 3 percent for ejection fraction and 6.5 percent for mean V_{CF}; the average variation for PEP/LVET was 9 percent. These figures are in accord with previous data from our laboratory showing that mean V_{CF} was reproducible within 6 percent when determined by echocardiography[3] and cineventriculography.[12]

Results

In the 48 patients, mean endocardial posterior wall velocity averaged 3.8 cm/sec (range 2.0 to 7.4) and correlated closely with maximal endocardial posterior wall velocity (average 4.6 cm/sec; range 2.9 to 8.7). In nine patients considered to have normal left ventricular function on the basis of hemodynamic studies, mean endocardial posterior wall velocity averaged 4.2 cm/sec (range 3.0 to 4.4) and maximal endocardial posterior wall velocity averaged 5.1 cm/sec (range 3.7 to 5.6). In the 39 patients with coronary artery disease, mean posterior wall velocity averaged 3.6 cm/sec (range 2.0 to 7.4) and the average maximal posterior wall velocity was 4.3 cm/sec (range 2.1 to 7.5). Neither mean nor maximal posterior wall velocity separated normal from impaired left ventricular performance.

Posterior wall velocity vs. ejection fraction: Figure 3 shows the poor correlation between mean endocardial posterior wall velocity and ejection fraction determined by echocardiogram and cineangiocardiogram. In 7 patients with a reduced ejection fraction by echocardiogram (<0.52), mean endocardial posterior wall velocity exceeded our lower limit of normal for mean posterior wall velocity (2.5 cm/sec, a value that is 2 standard deviations below the mean value derived from 24 normal subjects in our laboratory). Similarly, in five patients with a depressed ejection fraction by cineangiogram, mean endocardial posterior wall velocity was within the normal range. Use of maximal endocardial posterior wall velocity did not improve the separation of normal from abnormal left ventricular performance.

Posterior wall velocity vs. V_{CF}: Figure 4 shows the correlation between mean endocardial posterior wall velocity and mean V_{CF} determined by echocardiogram and cineangiocardiogram. Of 25 patients with a reduced mean V_{CF} (<1.05 circumferences/sec) by echocardiogram,[3] only 3 had a depressed mean endocardial posterior wall velocity (Fig. 4, left panel). Similarly, of 12 patients whose mean V_{CF} by cineangiogram was reduced (<1.2 circumferences/sec),[12] only 2 had an abnormal value for mean posterior wall velocity (Fig. 4, right panel). Substitution of maximal for mean endocardial posterior wall velocity did not improve the separation.

Posterior wall velocity vs. PEP/LVET: Equally poor results were obtained when mean endocardial posterior wall velocity was plotted against the ratio of preejection period (PEP) to left ventricular ejection time (LVET) (Fig. 5, left panel), and the preejection period was corrected for heart rate (PEPI, Fig 5, right panel). Of 23 patients with an abnormal PEP/LVET ratio (>0.420), 21 had a normal value for mean posterior wall velocity. In five patients PEPI was abnormal (>144 msec), but mean posterior wall velocity was within the normal range, whereas the converse was true in three patients.

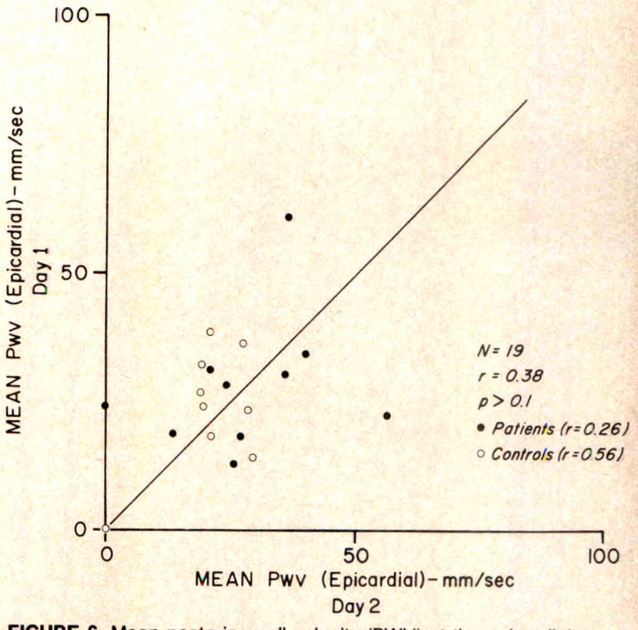

FIGURE 6. Mean posterior wall velocity (PWV) at the epicardial surface obtained on one day (Day 1) is plotted against mean epicardial posterior wall velocity measured on the next day (Day 2). Seven patients with myocardial infarction and three patients with angina pectoris **(closed circles)** and nine normal subjects **(open circles)** were studied. The **solid line** represents the line of identity.

Maximal epicardial posterior wall velocity (average 2.3 cm/sec, range 1.1 to 4.1) also failed to distinguish patients with normal left ventricular function (average 2.5 cm/sec, range 1.9 to 3.0) from those with reduced performance (average 2.2 cm/sec, range 1.1 to 4.1). This measure also failed to show significant correlation with mean endocardial posterior wall velocity, maximal endocardial posterior wall velocity, echocardiographic ejection fraction, echocardiographic mean V_{CF}, PEP/LVET, PEPI, cineangiographic ejection fraction, cineangiographic mean V_{CF} or heart rate.

Posterior wall velocity in acute myocardial infarction: Estimations of mean epicardial posterior wall velocity performed in 10 patients with acute myocardial infarction or angina pectoris studied in the coronary care unit also failed to distinguish patients from normal control subjects. Thus, mean epicardial posterior wall velocity averaged 2.27 cm/sec (range 0.5 to 4.4) in these patients, and 2.2 cm/sec (range 0.5 to 3.0) in nine normal control subjects. Furthermore, despite careful attention to consistent localization of the ultrasound beam, daily estimations of epicardial posterior wall velocity in individual subjects showed wide variation. Figure 6 depicts mean epicardial posterior wall velocity as measured on two successive days in the 10 patients hospitalized in the coronary care unit and in 9 normal control subjects. There is a disappointing correlation be-

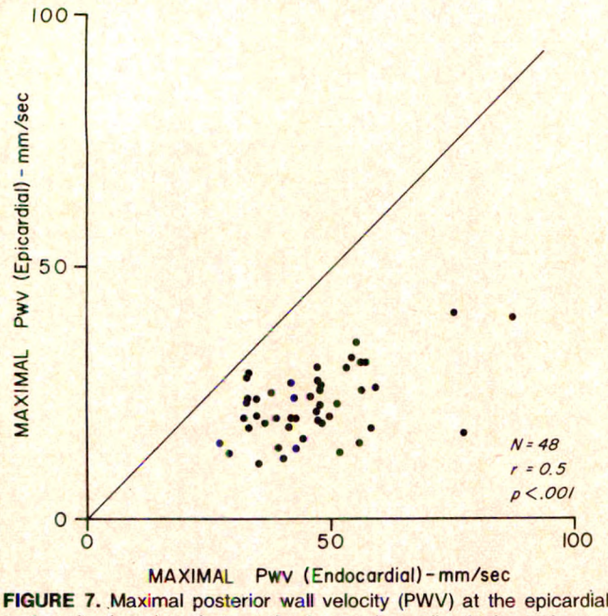

FIGURE 7. Maximal posterior wall velocity (PWV) at the epicardial surface is plotted against maximal posterior wall velocity at the endocardial surface in all 48 patients studied. The **solid line** represents the line of identity. In each instance, the endocardial velocity exceeds the epicardial velocity. Such a disparity is to be expected, since the posterior wall myocardium not only moves anteriorly, but also thickens during systole.

tween the paired measurements in each patient, indicating that the measurement of mean epicardial posterior wall velocity is poorly reproducible from day to day.

Similarly, endocardial posterior wall velocity is also a poorly reproducible measure. For example, in six patients, four of whom had normal left ventricular function, mean endocardial posterior wall velocity determined on 16 occasions varied by an average of 20.5 percent (range 6 to 52 percent) and maximal endocardial posterior wall velocity by an average of 15.8 percent (range 7.5 to 27 percent). Further, despite the use of only strictly satisfactorily recorded beats for calculation, there was a beat to beat variation in maximal endocardial posterior wall velocity averaging 42 percent (range 6.0 to 143 percent). These variations in endocardial posterior wall velocity occurred despite careful attention to visualization of the mitral valve supporting apparatus ("x"-line) as a landmark (Fig. 1).

Since epicardial posterior wall velocity is rapidly and easily obtainable by echocardiography, we compared this measure with endocardial posterior wall velocity, which is difficult and time-consuming to obtain, in all 48 patients. The results, shown in Figure 7, indicate a poor correlation between the two measures of posterior wall velocity.

Echographic and ventriculographic ejection fraction and V_{CF}: Highly significant correlations were obtained by comparing echocardiographic and ventriculographic estimations of ejection fraction. These values also correlated well with systolic time intervals, particularly the PEP/LVET ratio and the preejection period corrected for heart rate (PEPI). Thus echocardiographic ejection fraction (mean 0.61, range 0.21 to 0.83) correlated well with cineangiographic ejection fraction (mean 0.54, range 0.19 to 0.73; $r = 0.83$, $P < 0.001$); with PEP/LVET (mean 0.443, range 0.87 to 0.263; $r = -0.84$, $P < 0.001$) and with PEPI (mean 137.3 msec, range 81.0 to 186.0; $r = -0.71$, $P < 0.001$). Cineangiographic ejection fraction, in turn, was closely related both to PEP/LVET ($r = -0.77$, $P < 0.001$) and to PEPI ($r = -0.60$, $P < 0.005$).

Further, comparable estimates of mean V_{CF} were obtained from both the echocardiogram and the ventriculogram. Thus, echocardiographic mean V_{CF} (average 1.07 circumferences/sec, range 0.33 to 2.23) correlated with cineangiographic mean V_{CF} (average 1.1 circumferences/sec, range 0.33 to 2.28; $r = 0.70$, $P < 0.001$); with PEP/LVET ($r = -0.62$, $P < 0.001$) and with PEPI ($r = -0.70$, $P < 0.001$).

Discussion

Noninvasive techniques, such as ultrasound echocardiography and measurement of systolic time intervals, recently have been utilized to quantitate left ventricular function in man. Thus, echocardiographic determinations of both ejection fraction[1] and mean velocity of basal circumferential fiber shortening (mean V_{CF}[3]) previously have been reported to correlate well with standard cineangiographic estimates of these measures, and thereby to provide reliable estimates of left ventricular performance in the basal state. It has also been shown that the ratio of preejection period to left ventricular ejection time (PEP/LVET) correlates highly with cineangiographic determinations of ejection fraction[16] and that the preejection period corrected for heart rate (PEPI) reflects the contractile state of the ventricle during isovolumetric systole.[17] Systolic time intervals have also been reported to be of use in routine follow-up studies of patients who have had coronary bypass surgery, particularly in the documentation of early changes in left ventricular function before clinical deterioration occurs.[18]

However, ultrasound determinations of ejection fraction and mean V_{CF} require an operator highly experienced in the performance of echocardiography, considerable time and a cooperative, supine patient. These requirements may be difficult to meet in sick patients, especially those with acute myocardial infarction. Because the velocity of the posterior left ventricular epicardial surface is among the simplest of ultrasound measurements to obtain, it has been suggested that calculation of posterior wall velocity might provide a suitable alternative to more complex echocardiographic measurements of left ventricular function. Posterior wall velocity has been reported to reflect the velocity of circumferential fiber shortening[6] and to correspond to changes in left ventricular performance induced by physiologic and pharmacologic interventions,[6,7] and by acute myocardial infarction.[8]

Reliability and reproducibility of posterior wall velocity determinations: Our results indicated that measurement of posterior wall velocity did not correlate satisfactorily with either echocardiographic

or standard cineangiographic measurements of ejection fraction and mean V_{CF}. Equally poor results were obtained when posterior wall velocity was compared with measurement of systolic time intervals. Disappointing correlations were obtained whether posterior wall endocardium or epicardium was examined, or mean or maximal velocity calculated. The closest correlation observed was between mean endocardial posterior wall velocity and echocardiographic mean V_{CF} ($r = 0.70$), presumably because calculation of posterior wall excursion is part of the calculation of mean V_{CF} by this method. However, in 16 patients with wall motion abnormalities documented by cineangiography, mean endocardial posterior wall velocity was normal in 13 and echocardiographic mean V_{CF} was depressed in 15.

Our serial studies in 10 patients with acute myocardial infarction or angina pectoris who were hospitalized in the coronary care unit showed that both endocardial and epicardial posterior wall velocity vary widely from day to day, and from beat to beat in individual patients, despite careful efforts to achieve a consistent ultrasound beam plane by careful visualization of the mitral valve apparatus. Therefore, these measures appeared to be unreliable for assessment of basal left ventricular performance or changes in myocardial function produced by interventions.

In searching for a noninvasive measure of cardiac function that could be obtained rapidly and easily in the coronary care unit, we examined the velocity of movement of left ventricular posterior wall epicardium, since consistent definition of posterior wall endocardium is usually more difficult and time consuming. However, as indicated, this measure also did not distinguish normal from abnormal left ventricular performance, correlate significantly with other indexes examined, or demonstrate adequate reproducibility from beat to beat or day to day. Thus, we were unable to confirm the observation that abnormalities in the contour of the left ventricular posterior wall epicardial echo could be utilized to predict alterations in myocardial function.[6]

Reasons for unreliability of posterior wall velocity as an index of myocardial performance: In comparison with other measures of myocardial performance, the values for posterior wall velocity generally tended to overestimate left ventricular function. Furthermore, despite the inability of posterior wall velocity to provide accurate information on total left ventricular performance in patients with coronary heart disease, ultrasound estimates of other ejection phase indexes of myocardial function, particularly mean V_{CF}, remain highly comparable to cineangiographic measurements.[19] Why posterior wall velocity is unreliable and mean V_{CF} accurate may be explained as follows: (1) Despite accurate localization and consistent examination of one area of the posterior left ventricular wall, and despite use of the same cycles for determination of both mean V_{CF} and posterior wall velocity, it is probable that in patients with coronary artery disease such an area is unrepresentative of the left ventricular myocardium as a whole. This is so because the posterior wall is an uncommon site for the localization of ischemic damage in comparison with the anterior, lateral, inferior or apical segments of the left ventricle, and the motion of these segments is entirely ignored in the determination of posterior wall velocity. (2) It has been our observation that when excursion of one of the ventricular walls is reduced because of ischemia or fibrosis, some compensation frequently is provided by increased excursion of the opposing wall, so that any error introduced by measurement of movement of one wall tends to be canceled by that of the other.

McDonald et al.[20] have recently described the influence on the echocardiogram of the anterior motion of the whole heart during systole. This systolic anterior motion diminishes the recorded posterior excursion of the interventricular septum and, conversely, increases the recorded anterior movement of the posterior left ventricular wall. This effect of the anterior motion of the whole heart during systole tends to be nullified when both septal and posterior wall movement are measured in the echocardiographic estimation of left ventricular dimensions, but it may lead to exaggeration of calculated posterior wall velocity.

The results of our study are in agreement with the recent observations of Fogelman et al.,[21] who found no consistent abnormalities in the rate of systolic motion of the posterior left ventricular wall during exercise-induced angina pectoris. They also reported that early diastolic motion of the posterior wall was reduced only during stress-induced angina.[21] In our study we did not examine patients with valvular heart disease or nonischemic cardiomyopathy. Although the possibility remains that in such patients estimation of posterior wall velocity might provide useful information on total left ventricular performance, Belenkie et al.[22] recently demonstrated that mean posterior wall velocity correlated poorly with other ultrasound and cineangiographic measures of left ventricular performance in 20 patients with valvular heart disease and in 3 subjects with nonischemic cardiomyopathy.

We conclude that despite its ease and speed of performance, calculation of posterior wall endocardial or epicardial velocity, whether derived as a mean or maximum, is unreliable for basal or serial assessment of total left ventricular performance in patients with ischemic heart disease.

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Mortality in Patients Undergoing Coronary Artery Bypass Surgery After Myocardial Infarction

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Data on 1,700 patients who underwent coronary artery bypass surgery without additional cardiovascular procedures at the Texas Heart Institute were analyzed, relating the interval between myocardial infarction and operation to early mortality (within 30 days after operation). Patients who underwent coronary artery bypass surgery after a recent infarction (within 2 months before operation) had a higher rate of early mortality (14.5 percent) than patients who had an old infarction (6.9 percent) or no previous infarction (4.1 percent). The interval between recent infarction and operation was most significant. Mortality in patients who underwent operation within the first 7 days after acute infarction (38.1 percent) was more than six times greater than in patients who were operated on 31 to 60 days after infarction (5.8 percent). Mortality of those operated on 8 to 30 days after infarction was 16.4 percent. Elective coronary artery bypass surgery after recent infarction is best accomplished after the first 30 days, when there is no increased risk to the patient. Emergency coronary artery bypass after complicated acute myocardial infarction may be a lifesaving procedure, but it is associated with increased early mortality and should be reserved for those whose condition has not responded to aggressive medical therapy.

Evaluation of patients who have undergone coronary artery bypass procedures has elucidated factors associated with higher rates of early mortality. In previous reports,[1,2] we presented data that define these factors, which include advanced age, female sex, higher coronary artery scores (by the method of Friesinger et al.),[3] the presence of congestive heart failure, increased left ventricular diastolic pressure, significant left ventricular dysfunction, lesions of the left main coronary artery, concomitant endarterectomy with bypass, associated valvular lesions and recent acute myocardial infarction before operation. This report further analyzes the relation between recent myocardial infarction and early (within 30 days after operation) mortality after coronary artery bypass surgery.

Material and Methods

During a 39 month period ending December 1972, a total of 1,944 patients underwent aortocoronary saphenous vein bypass surgery at the Texas Heart Institute. Of these, 1,700 patients who had no additional cardiovascular procedures, except for concomitant endarterectomy, were classified into three groups: Patients in Group 1 had no previous infarction according to electrocardiogram and history; patients in Group 2 had old myocardial infarction more than 2 months before operation, as determined by electrocardiogram or history, or both; and patients in Group 3 had a recent myocardial infarction within 2 months before operation, as documented by electrocardiogram, history and serum enzyme determinations. Electrocardiographic changes in all three groups included development of new Q waves in all but two patients. Patients in Group 3 were closely analyzed for exact intervals between infarc-

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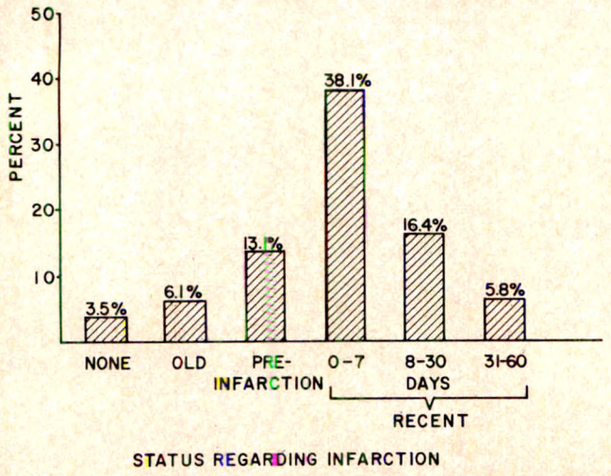

FIGURE 1. Early mortality rates in patients undergoing coronary artery bypass surgery, in relation to interval between infarction and operation.

tion and operation. The results relating to early mortality were tabulated in all groups. Most of the patients underwent total cardiopulmonary bypass with ischemic cardiac arrest. During the latter part of this study general body hypothermia and direct cooling of the heart with cold saline solution were used for patients undergoing multiple bypass procedures. Intraaortic balloon counterpulsation and emergency femoral vein to artery partial bypass were employed before thoracotomy in selected cases.

Results

The overall early mortality rate in the total group of 1,700 patients was 6.9 percent (118 deaths). The early mortality rate of patients who had no previous infarction (Group 1) was 4.1 percent (15 deaths among 361 patients). In Group 2, patients with old myocardial infarction, the early mortality rate was 6.9 percent (82 deaths among 1,194 patients). There were 145 patients who had a myocardial infarction within 2 months before operation (Group 3), and 21 of these patients died in the early postoperative period (early mortality rate 14.5 percent).

Further classification of the patients in Group 3 according to the time interval from infarction to operation revealed marked differences in the mortality of the subgroups. Patients who underwent coronary artery bypass surgery within 7 days after a recent myocardial infarction had a 38.1 percent mortality rate. There were no significant differences between the early mortality rate of those who were operated on within the first 24 hours after acute infarction (36.4 percent) and those who were operated on within 2 to 7 days after acute infarction (40 percent). The early mortality rate of patients who had coronary artery bypass surgery within 8 to 30 days after acute infarction was 16.4 percent; the rate was 5.8 percent in patients operated on within 31 to 60 days after acute infarction. Figure 1 demonstrates the more than sixfold greater early mortality in patients who underwent operation within 7 days after acute infarction than in those who underwent operation 31 to 60 days after infarction.

Coronary artery bypass within 24 hours after acute infarction: Table I lists the 11 patients who underwent operation within the first 24 hours after acute infarction. The period from infarction to thoracotomy was estimated to the closest half hour. Pa-

TABLE I

Patients with Coronary Artery Bypass (CAB) Performed Within 24 Hours After Infarction

Case no.	Age (yr) & Sex	Interval (hr)*	Status Before Surgery	Surgery	Outcome
1	53M	2	Postcardiac arrest; hypotension	Triple CAB with hypothermia	Transient hypotension and ventricular arrhythmias
2	58M	2	Multiple cardiac arrests	Triple CAB with hypothermia	No significant complications
3	65M	2	Severe heart failure	Triple CAB with hypothermia	No significant complications
4	69M	3	Postcardiac arrest	Single CAB	No significant complications
5	42M	3.5	Stable	Double CAB	Cardiac arrest with successful resuscitation
6	49F	16	Multiple cardiac arrests; hypotension	Double CAB†	Transient poor cardiac output
7	37F	17	Stable	Single CAB	No significant complications
8	49M	1	Postcardiac arrest	Single CAB†	Died in operating room; no effective cardiac output
9	52M	2	Postcardiac arrest; severe heart failure	Double CAB†	Died in operating room; no effective cardiac output
10	64M	4.5	Multiple cardiac arrests; cardiogenic shock	Double CAB†‡	Died in operating room; no effective cardiac output
11	49M	21	Severe heart failure	Single CAB	Died in operating room; no effective cardiac output

* Time interval between infarction and thoracotomy.
† Femoral partial bypass before thoracotomy.
‡ Intraaortic balloon counterpulsation.

tient 8 underwent thoracotomy within 65 minutes after acute cardiac arrest associated with acute myocardial infarction. Seven of the 11 patients in this group had a myocardial infarction during or shortly after cardiac catheterization. In most cases these patients before operation manifested cardiac arrest, severe heart failure, hypotension or frank cardiogenic shock complicating an acute infarction. Only two patients underwent coronary artery bypass after an uncomplicated infarction that occurred at the time of catheterization. Four patients died, all of whom had a complicated infarction. Three of the four who died (Patients 8, 9 and 10) had severe lesions of the left main coronary artery. All four patients died in the operating room with an essentially noncontractile left ventricle.

Coronary artery bypass within 2 to 7 days after acute infarction: Ten patients underwent coronary artery bypass surgery 2 to 7 days after acute infarction. Seven of these patients had a complicated infarction: Three had severe congestive heart failure and four had extension of the infarction. Three patients had an uncomplicated infarction. Four of the 10 patients in this group died in the early postoperative period. Three of these patients had a complicated myocardial infarction.

Coronary artery bypass between 8 and 30 days after acute infarction: Fifty-five patients underwent coronary artery bypass surgery 8 to 30 days after acute infarction. Almost half of these patients had complications of infarction including cardiac arrest, extension of infarction or persistent pain at rest. There were five early deaths among those with a complicated infarction and four early deaths among those who had uncomplicated infarction.

Coronary artery bypass between 31 and 60 days after acute infarction: Sixty-nine patients underwent coronary artery bypass surgery 31 to 60 days after acute infarction. Only one fourth of these patients had complications of infarction including extension of infarction, recurrent pain at rest or cardiac arrest. There were two deaths among these patients with a complicated infarction and two deaths among the patients with an uncomplicated infarction.

Effect of preinfarction angina on early mortality after coronary artery bypass: One additional factor that had a very significant effect on early mortality was the presence of preinfarction angina. We have reserved the term "preinfarction angina" for patients with prolonged pain at rest without transmural infarction, and have not included patients with crescendo angina or other unstable anginal patterns. Of 137 patients who met this criterion of preinfarction angina, 18 died in the early period after operation (13.1 percent). When these patients with preinfarction angina are subtracted from Groups 1 and 2, the lower mortality figures of 3.5 and 6.1 percent are found in the remaining patients of Groups 1 and 2, respectively. Figure 1 displays the early mortality of each of the clinical subgroups. It is apparent that the risk of surgery during the first 7 days after infarction far exceeds that of any of the clinical situations presented. It is also apparent that early mortality in patients who undergo operation later than the first 30 days after an acute myocardial infarction is no greater than in those who experience an infarction more than 2 months before operation.

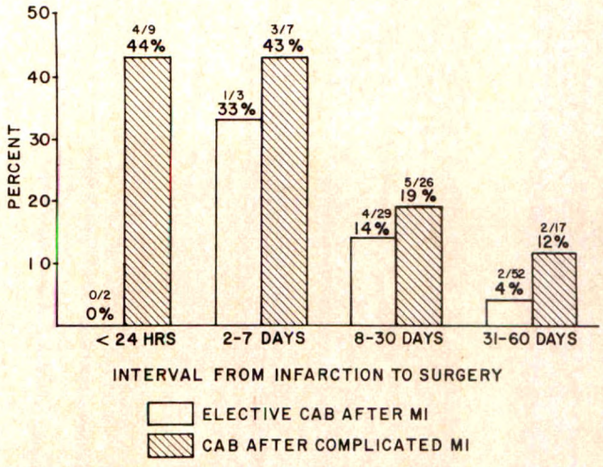

FIGURE 2. Early mortality rates in patients undergoing coronary artery bypass surgery (CAB) after recent myocardial infarction (MI), in relation to indications for surgery.

Discussion

Surgical procedures performed after a recent myocardial infarction are accompanied by a high mortality rate. In 1964, Arkins et al.[4] reported a 40 percent mortality rate among patients who underwent general surgical procedures within 3 months after acute myocardial infarction. The mortality rates of patients undergoing coronary artery bypass surgery after an established myocardial infarction have ranged from 0 to 80 percent in previous reports.[5–9] Our data suggest that revascularization can be performed after the first 30 days without an increase in early mortality. During the first 30 days, and especially during the first week after infarction, the mortality rate of patients undergoing coronary artery bypass is very high and suggests that the beneficial effects of revascularization do not overcome the risks of surgery in a patient with an area of myocardial necrosis.

Myocardial revascularization within the first few hours after coronary occlusion has been experimentally demonstrated to have beneficial effects by decreasing the area of myocardial necrosis and saving ventricular function.[10] After several hours have elapsed, there remains no theoretical benefit of early revascularization and, in the patient whose condition is stable, there is no reason to consider operation within the first 30 days after infarction.

Mortality related to indications for surgery: Figure 2 shows the mortality rates of patients operated on after complicated and uncomplicated myocardial infarction according to the interval between infarction and coronary artery bypass surgery. High mortality rates were noted in all patients after a complicated infarction. Patients operated on within the first 7 days experienced twice the mortality of those operated on 8 to 30 days after infarction and more

than three times the mortality of those operated on more than 30 days after complicated myocardial infarction. The more severe complications, including shock and severe heart failure, were present only in patients operated on less than 31 days after infarction. The numbers are too small in the first two subgroups of patients operated on after uncomplicated myocardial infarction to draw definite conclusions. The early mortality of all patients (after stable or unstable myocardial infarction) undergoing coronary artery bypass within the first 30 days after infarction is statistically greater than the mortality in the second month after an acute myocardial infarction ($P < 0.01$; chi-square = 8.03).

A significant factor that must be considered in assessing the high mortality rates is the large number of patients who underwent operation as a resuscitative attempt in the early postinfarction period.

Clinical implications: From our experience with patients undergoing coronary artery bypass after recent myocardial infarction, we make the following conclusions: (1) Coronary artery bypass performed after a recent myocardial infarction is associated with a high rate of early mortality. (2) Elective coronary artery bypass after a stable recent infarction is best accomplished after the first 30 days, when there is no increased risk to the patient. (3) Emergency coronary artery bypass after complicated acute myocardial infarction may be a life-saving procedure; however, it is associated with a high early mortality rate and should be reserved for those in whom aggressive medical therapy is unsuccessful.

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Lidocaine-Induced Heart Block in Patients with Bundle Branch Block

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His bundle electrography and atrial pacing were used to evaluate the effect on cardiac conduction of an intravenous bolus injection (50 to 100 mg) of lidocaine in 21 patients with various intraventricular conduction abnormalities and ventricular premature beats. Sixteen patients (76 percent) had prolonged His-Purkinje conduction time (H–V interval greater than 55 msec). Six patients (all with a prolonged H–V interval) had earlier shown transient second degree or complete heart block. Administration of lidocaine produced complete heart block distal to the His bundle potential in two patients. Both patients had a prolonged H–V interval (100 and 140 msec, respectively) and had shown 2:1 A–V block distal to the H deflection on atrial pacing before the injection. A third patient, with an H–V interval of 70 msec, showed second degree block distal to the H deflection during atrial pacing after administration of lidocaine but not before. An additional patient, observed clinically to have alternating right and left bundle branch block, experienced cardiac standstill after the injection. Lidocaine should be used cautiously in patients with incomplete bilateral bundle branch block, and a temporary pacemaker should be considered in patients with a prolonged H–V interval or known trifascicular disease.

Lidocaine, one of the commonest antiarrhythmic drugs used today, is the drug of choice in the initial treatment of ventricular premature beats.[1–8] The efficacy of lidocaine in treating atrial arrhythmias has also been reported but is not well established. Therapeutic doses of lidocaine have minimal effects on cardiac hemodynamics and may produce minor side effects such as paresthesia, confusion and lightheadedness. Sinus bradycardia and heart block have been considered contraindications for the use of lidocaine. In this study we evaluated the effect of lidocaine on cardiac conduction in 21 patients with various forms of intraventricular conduction abnormalities and ventricular premature contractions.

Methods and Material

The study group consisted of 21 patients with various forms of intraventricular conduction abnormalities and ventricular premature beats. Fifteen were male and six female; their ages ranged from 48 to 89 years. None of the patients had acute myocardial infarction; patients with clinical evidence of congestive heart failure and liver disease were excluded. Sixteen patients had an electrocardiographic pattern of right bundle branch block and left anterior hemiblock (mean frontal plane QRS axis greater than −30°). Four had a pattern of right bundle branch block and left posterior hemiblock (mean frontal plane QRS axis greater than +100°) and one a pattern of complete left bundle branch block. Twenty patients had sinus rhythm and one had atrial fibrillation. When studied, all patients with sinus rhythm had 1:1 atrioventricular (A–V) conduction although six had earlier shown transient Mobitz type II or complete heart block.

The nature and purpose of the study were explained and consent of the patients was obtained. His bundle electrograms were recorded by the method of

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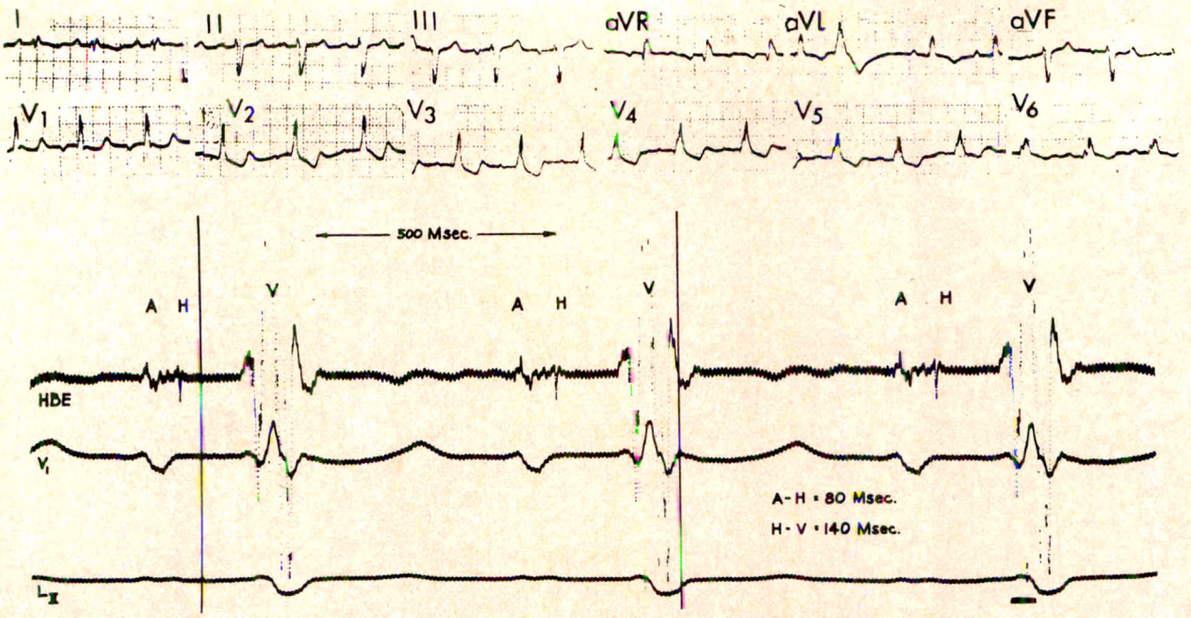

FIGURE 1. Case 2. Twelve lead electrocardiogram with base-line His bundle electrogram (HBE).

Scherlag et al.[9] A no. 6 bipolar electrode catheter with interelectrode distance of 1 cm was passed percutaneously by way of a femoral vein and, under fluoroscopic control, the tip was advanced until it lay across the tricuspid valve. His bundle electrograms were recorded on an EEP channel of an Electronics for Medicine multichannel recorder at paper speeds of 75 to 150 mm/sec with a frequency response of 40 to 500 Hz. One or more leads of the peripheral electrocardiogram were recorded simultaneously. In 15 patients atrial pacing was performed by a second catheter positioned against the lateral wall of the right atrium. The pacing rate was increased gradually to a maximum of 150/min or until second degree A–V block appeared. Lidocaine (50 mg in 10 patients and 100 mg in 11 patients) was administered intravenously after the base-line studies. A trial pacing was repeated 5 minutes after injection of lidocaine.

Results

The A–H interval was within normal limits (70 to 140 msec) in all 20 patients with sinus rhythm and did not change significantly after administration of lidocaine. The H–V interval was prolonged (greater than 55 msec) in 16 patients (76 percent). In four, the prolongation was marked (greater than 95 msec). Second degree A–V block appeared in 9 of 15 patients during atrial pacing. In six, the block was at the A–V node, and in three it was distal to the H deflection. After injection of lidocaine, two patients showed spontaneous high grade and complete A–V block lasting for several seconds. Block in each instance was localized distal to the H deflection, and instantaneous ventricular pacing was achieved in both cases. Both patients had a significantly prolonged H–V interval (100 and 140 msec, respectively) and had shown second degree block distal to the H deflection during atrial pacing before injection of lidocaine. A third patient, with an H–V interval of 70 msec, had 1:1 A–V conduction with atrial pacing before administration of lidocaine and second degree block distal to the H deflection when atrial pacing was repeated after administration. Another patient had a 5 to 10 msec increase in the H–V interval after injection of lidocaine.

Illustrative Cases

Case 1: This case has previously been reported by us[10] and will be discussed briefly. The patient is an 83 year old man who was seen in the emergency room because of palpitations and weakness. The electrocardiogram revealed sinus rhythm with right bundle branch block, left anterior hemiblock and many ventricular premature systoles. A 50 mg bolus injection of lidocaine produced high grade and then complete heart block lasting for 20 seconds with spontaneous return to 1:1 A–V conduction. Because of this episode of block and the continuing indication for lidocaine, a temporary transvenous pacemaker was inserted. A His bundle electrogram recorded at this time showed an A–H interval of 90 msec and an H–V interval of 100 msec. Atrial pacing at a rate of 130/min produced 2:1 block distal to the H deflection; 1:1 A–V conduction promptly returned when atrial pacing was discontinued. Injection of 50 mg of lidocaine resulted in a transient period of 2:1 A–V block followed by complete A–V block distal to the H deflection. Instantaneous ventricular pacing was achieved during the episode of complete heart block. A permanent pacemaker was advised, but refused by the family.

Case 2: A 63 year old man was admitted because of increasing angina pectoris. He gave a history of several episodes of dizziness but denied syncope. The electrocardiogram on admission showed complete right bundle branch block with left anterior hemiblock. Transient high grade block was noted on a cardiac monitor, and a temporary transvenous pacemaker was immediately inserted. The His bundle electrogram recorded during antegrade conduction showed an A–H interval of 80 msec and an H–V interval of 140 msec. Atrial pacing at a rate of 120/min produced 2:1 block distal to the H deflection with prompt return to 1:1 A–V conduction at the termination of atrial pacing. A 50 mg bolus injection of lidocaine resulted in an increase of the H–V interval to 180 msec with progression to transient high grade block distal to the H deflection. The block disappeared spontaneously in 10 seconds. A permanent transvenous demand pacemaker was implanted subsequently.

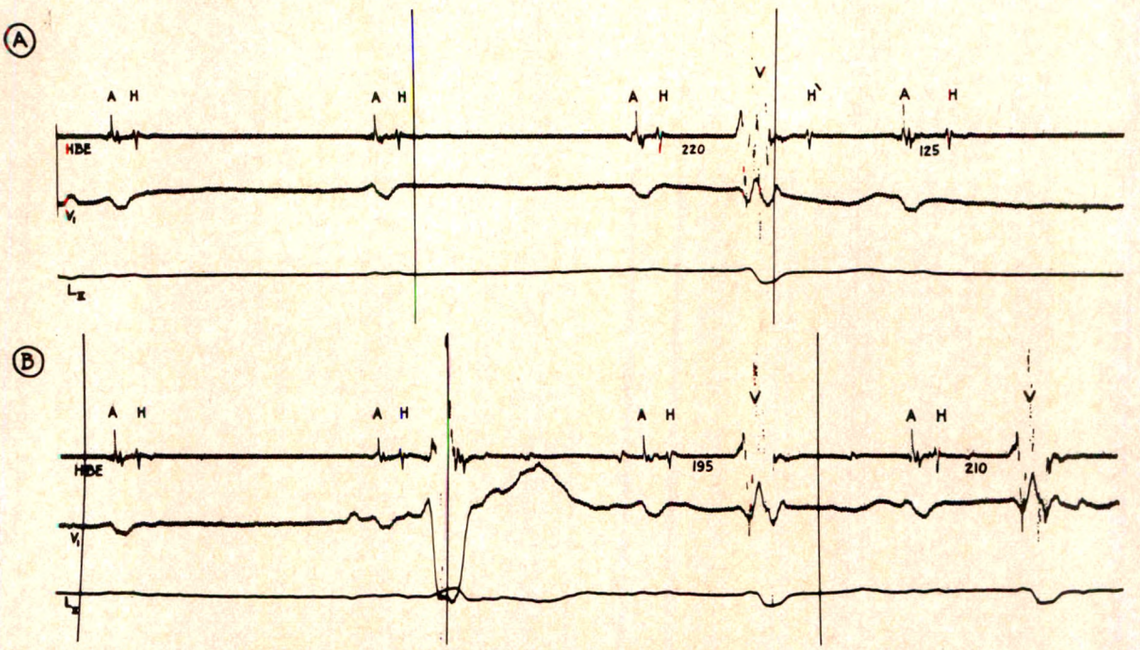

FIGURE 2. Case 2. His bundle recordings after administration of lidocaine (50 mg intravenously) show high grade A–V block distal to the H deflection. The H–V interval of the conducted beats is shown in the H–V segment. **A** and **B** are continuous strips.

Interpretation of electrocardiogram and His bundle electrogram: Figure 1 shows a 12 lead electrocardiogram obtained from this patient. The rhythm is sinus with a P–R interval of 0.24 second. The QRS complexes have a pattern of right bundle branch block and left anterior hemiblock. A ventricular premature beat is seen in lead aVL. In the baseline His bundle electrogram (Fig. 1, bottom) the A–H interval of 80 msec is within normal limits but the H–V interval is prolonged to 140 msec. Panels A and B in Figure 2 are continuous strips recorded after intravenous injection of 50 mg of lidocaine. Many nonconducted P waves are seen with block distal to the H deflection. The only QRS deflection in panel A and the last two QRS deflections in panel B are conducted beats with H–V intervals of various lengths. The first QRS deflection in panel B is a ventricular escape beat. A sharp spike marked H′ is seen after the ventricular depolarization in panel A. This is possibly a premature His bundle depolarization that is blocked antegrade. However, its retrograde conduction into the A–V node is evident from the prolongation of the next A–H interval to 125 instead of the normal 80 msec.[11] The possibility that this H′ spike represents a His bundle echo caused by prior ventricular depolarization cannot be ruled out since the previous beat has a long H–V interval.

Case 3: A 78 year old woman was admitted with a history of syncope. The electrocardiogram on admission revealed complete A–V block with wide idioventricular complexes at a rate of 32/min. A temporary endocardial pacemaker was immediately inserted. Antegrade 1:1 conduction reappeared soon after admission and persisted throughout the

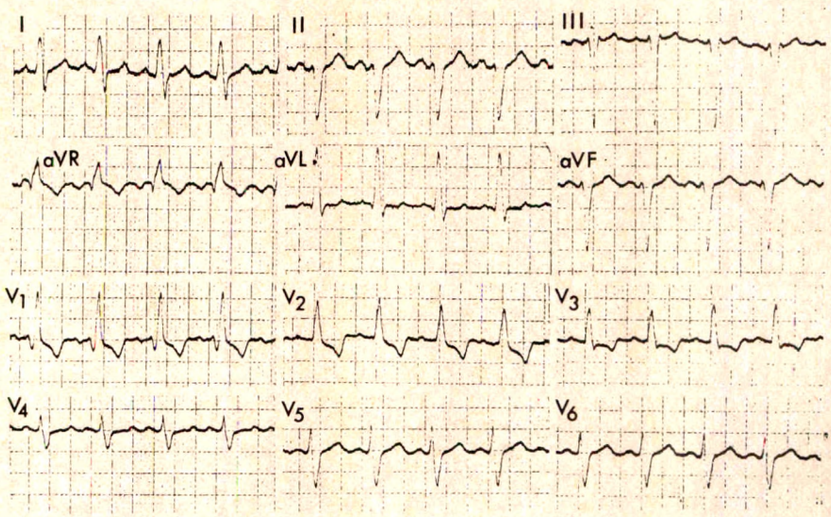

FIGURE 3. Case 3. Twelve lead electrocardiogram obtained before the study reveals right bundle branch block with left anterior hemiblock.

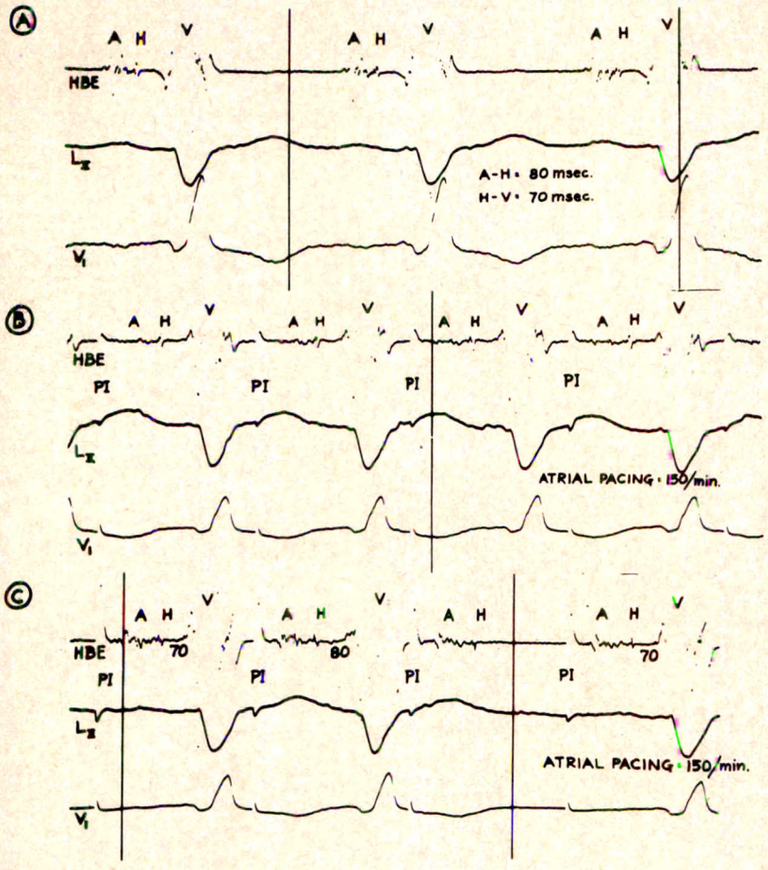

FIGURE 4. Case 3. **A,** base-line His bundle electrogram (HBE). **B,** 1:1 A–V conduction persists during atrial pacing at 150/min. **C,** atrial pacing at 150/min after administration of lidocaine produces Wenckebach type block distal to the H deflection. The H–V interval is shown in the H–V segment of the conducted beats. PI = pacing impulse.

hospital course. The electrocardiogram recorded during antegrade conduction showed right bundle branch block and left anterior hemiblock with ventricular premature beats. A His bundle electrogram recorded at that time showed an A–H interval of 80 and an H–V interval of 70 msec. Atrial pacing at 150/min produced a 1:1 A–V response. After intravenous injection of 100 mg of lidocaine, 1:1 A–V conduction persisted. However, when atrial pacing at 150/min was repeated, Wenckebach type second degree block appeared distal to the His bundle potential; the 1:1 A–V conduction returned when pacing was stopped. The patient underwent implantation of a permanent transvenous demand pacemaker 1 week after the study.

Interpretation of electrocardiogram and His bundle electrogram: The 12 lead electrocardiogram of this patient is shown in Figure 3. The rhythm is sinus with 1:1 A–V conduction and a P–R interval of 0.18 second. A pattern of complete right bundle branch block with left anterior hemiblock is present. Panel A in Figure 4 shows the His bundle electrogram during sinus rhythm. The H–V interval is 70 msec. In panel B, the effect of atrial pacing at a rate of 150/min is shown; the 1:1 A–V conduction persists and the H–V interval remains unchanged. Panel C illustrates the effect of atrial pacing at a rate of 150/min after intravenous administration of 100 mg of lidocaine. The H–V interval progressively increases from 70 to 80 msec and then one beat is blocked distal to the H deflection. This is an example of Wenckebach type block distal to the H deflection and has been reported previously.[12–14]

Case 4: An 84 year old woman, who was admitted with a chief complaint of pain in the right side of the chest, was not among our study group. Her electrocardiogram revealed atrial fibrillation with moderate ventricular response and complete left bundle branch block. Intermittent complexes with a right bundle branch block pattern were noted and thought to be premature ventricular beats. Twenty-four hours after admission, the frequency of these abnormal complexes had increased; the patient was given 100 mg of lidocaine intravenously because she was thought to have a ventricular arrhythmia. Twenty seconds after this injection, there was marked slowing of the ventricular rate followed by asystole with occasional ventricular escape beats. The patient was resuscitated and ventricular pacing was initiated, but she died several hours later.

Interpretation of electrocardiogram: Figure 5, a 12 lead electrocardiogram obtained from this patient, reveals atrial fibrillation and a moderate ventricular response. A pattern of left bundle branch block is evident, with the first beat in lead V_1 suggesting right bundle branch block. Strips A to F are continuous and show the effect of intravenous injection of 100 mg of lidocaine. Alternating left and right bundle branch block are seen in strips A to C. Slowing of the ventricular rate with complete asystole is evident in strips D to F.

Discussion

The effect of lidocaine on atrioventricular and intraventricular conduction has been evaluated in the experimental animal.[15] Lidocaine in therapeutic doses had no significant effect on A–V nodal and His-Purkinje conduction in dogs[15]; however, a prolonga-

tion of the A–V nodal conduction time was seen after administration of large doses. In canine ventricular muscle-Purkinje fiber preparations, lidocaine in a concentration comparable to in vivo therapeutic levels produced a slight increase in conduction velocity of the Purkinje tissue and caused marked acceleration of conduction through the ventricular muscle-Purkinje fiber junction.[16] In the same experiment, a further increase in the concentration of lidocaine slowed the conduction in the Purkinje tissue. Lidocaine in therapeutic doses has also been found to abolish decremental conduction and reduce the block at the ventricular muscle-Purkinje fiber junction.[17]

Using His bundle electrography and atrial pacing, Rosen et al.[18] studied the effect of lidocaine on cardiac conduction in 10 patients with heart disease. Only two of these patients had a QRS duration of more than 0.12 second. There was no significant change in the A–V nodal and His-Purkinje conduction time after administration of lidocaine. In a similar study, Bekheit et al.[19] found no significant change in the A–H or H–V interval after administration of lidocaine.

Heart block secondary to administration of lidocaine: Gianelly et al.[1] described two cases of heart block secondary to administration of lidocaine. In one case the block was probably due to acute inferior wall myocardial infarction since it persisted for several days after cessation of lidocaine infusion. In the second case second degree block progressed to complete heart block after the infusion. Since the type of block and the QRS configuration were not described, it is not possible to locate the site of block in this patient. More recently, Josephson et al.[20] described a patient with left bundle branch block and an H–V interval of 50 msec. After an infusion of 100 mg of lidocaine, the patient experienced several seconds of complete heart block. The block was localized at the A–V node by His bundle electrography. However, since the H–V interval had increased to 95 msec on return of antegrade conduction, the possibility of the proximal His bundle segment as the site of block cannot be ruled out. Liss et al.[21] in a recent brief communication described a patient with right bundle branch block and left axis deviation who had cardiac standstill after injection of lidocaine.

Our study was initiated to test the safety of lidocaine as an antiarrhythmic drug in patients with bundle branch block and premature ventricular beats. Most of the patients studied by Rosen and Bekheit and their co-workers[18,19] had a normal QRS configuration; by contrast, all of our patients had bundle branch block and 76 percent had trifascicular disease manifested by a prolonged H–V interval.[13,14,22,23] The extent of their conduction abnormality is further shown by the earlier transient second degree or complete heart block that occurred in six patients. Our Patients 1 and 2 had a markedly prolonged H–V interval (100 and 140 msec, respectively) and block occurred spontaneously after administration of lidocaine. In both, 2:1 A–V block indicative of advanced disease of the conduction system occurred distal to the H deflection during atrial pacing before administration of lidocaine. In Case 3 the H–V interval was only slightly prolonged (70 msec), and the stress of atrial pacing was necessary to induce block after injection of lidocaine. Patient 4 was observed clinically and was not in our study group. The beats with right bundle branch block were thought to be ventricular premature contractions (the reason the patient received lidocaine). In retrospect, this patient showed alternating left and right bundle branch block, thus fulfilling another criterion for trifascicular block.[22]

The results of our study suggest that lidocaine in therapeutic doses may not affect intraventricular conduction time in the majority of patients with bundle branch block. An occasional patient with more advanced trifascicular disease may have block distal to the His bundle potential after administration of lidocaine. It is possible that therapeutic doses of lido-

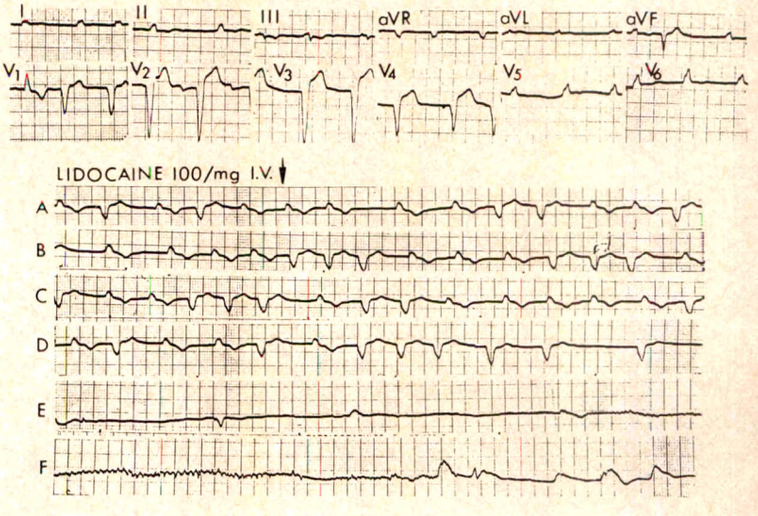

FIGURE 5. Case 4. Atrial fibrillation with ventricular response averaging 75/min is present in the 12 lead electrocardiogram **(top).** The QRS configuration is consistent with complete left bundle branch block. The first beat in lead V_1 shows a right bundle branch block configuration. A continuous lead V_1 rhythm strip is shown from **A** to **F.** Complexes with right and left bundle branch block are present. Marked slowing with cardiac standstill is present during the later part of strip **D** and in strips **E** and **F.**

caine are in fact toxic to these patients and that their already abnormal conduction system is further jeopardized with resultant heart block. Although gross heart failure was not evident in our patients, subclinical congestive heart failure could not be ruled out. Delayed metabolism secondary to heart failure may have resulted in toxic blood levels of lidocaine.[24] Determinations of blood levels of lidocaine will be necessary to study this hypothesis. Another possibility is that lidocaine depresses cardiac function and produces a transient reduction in cardiac output.[25] If this were true, a decrease in coronary perfusion might further slow conduction in the abnormal conduction system and result in heart block.

Clinical implications: We conclude that lidocaine should be administered cautiously to patients with incomplete bilateral bundle branch block. Patients with known H–V prolongation and intermittent high grade block are at greater risk and should be considered for temporary pacemaker insertion before treatment with lidocaine.

Acknowledgment

We thank Drs. H. Liu, M. Sayeed and E. Badui for help during various phases of this study. Mrs. D. Kren performed the artwork, and the secretarial assistance of Mrs. E. Erick and Ms. F. Schlesinger is deeply appreciated.

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Improved Intraventricular Conduction of Premature Beats After Diphenylhydantoin

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To determine the effect of diphenylhydantoin on intraventricular conduction in man, we utilized His bundle recordings and coupled atrial pacing to record the relative refractory period of the His-Purkinje system and the functional refractory period of the atrioventricular (A–V) node in 14 patients before and after administration of diphenylhydantoin at a rate of 50 mg/min. Before infusion of diphenylhydantoin (5 mg/kg at a rate of 50 mg/min) His-Purkinje conduction delay occurred with right bundle branch block in nine patients and with left bundle branch block in five patients. After infusion of diphenylhydantoin the onset or degree of His-Purkinje delay was altered in all patients. In nine patients diphenylhydantoin reduced the relative refractory period of the His-Purkinje system to a value less than that of the functional refractory period of the A–V node so that His-Purkinje conduction delay could not be demonstrated after diphenylhydantoin. In five patients, diphenylhydantoin reduced the relative refractory period of the His-Purkinje system or altered the degree of aberrant conduction, or both. Diphenylhydantoin reduced the minimal H_1–H_2 interval achieved before the onset of His-Purkinje block from 421 ± 27 (standard deviation) to 384 ± 34 msec ($P < 0.01$). The functional refractory period of the A–V node was decreased from a control value of 389 ± 39 to 374 ± 26 msec after administration of diphenylhydantoin, but the effect was not statistically significant ($P > 0.1$). These results establish that diphenylhydantoin has a significant effect on intraventricular conduction in man.

In 1950 diphenylhydantoin was reported to reverse experimental ventricular tachycardia produced by coronary arterial ligation,[1] and in 1954 it was shown to be effective in abolishing ouabain-induced ventricular tachycardia in dogs.[2] Subsequent clinical experience confirmed the antiarrhythmic properties of diphenylhydantoin and its value in the treatment of some instances of ventricular tachycardia and ventricular arrhythmias induced by digitalis.[3–6]

With the introduction of His bundle recording, interest has focused on the electrophysiologic actions of diphenylhydantoin. Although some types of ventricular arrhythmias respond favorably to diphenylhydantoin, initial reports have suggested that the drug has no effect on intraventricular conduction in man as measured by a stable interval from the His bundle potential to the onset of ventricular depolarization (H–V interval) during atrial pacing with a fixed cycle length.[7–9] The purpose of this study was to determine the effect of diphenylhydantoin on intraventricular conduction in man utilizing the introduction of premature atrial beats and measurements of the refractory periods of the His-Purkinje conduction system.[10,11] The results demonstrate a significant effect of diphenylhydantoin on intraventricular conduction in man. An abstract of these findings has been published previously.[12]

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TABLE I

Results of Conduction Studies

Case no.	Age (yr)	Diagnosis	A–H Time* (msec)		H–V Time* (msec)		Functional Refractory Period of A–V Node (msec)	
			Control	DPH	Control	DPH	Control	DPH
1	66	ASHD	70	65	40	40	400	350
2	38	ASHD	90	90	65	65	380	380
3	61	Normal	57	57	55	55	420	380
4	66	ASHD	62	75	50	50	390	395
5	63	ASHD	65	59	55	55	330	330
6	43	ASHD	65	60	50	50	385	375
7	53	ASHD	70	65	75	75	370	370
8	54	ASHD	85	85	45	45	380	395
9	29	Normal	65	50	50	50	360	360
10	51	ASHD	90	80	35	35	420	420
11	54	ASHD	90	70	45	45	420	410
12	54	ASHD	100	100	45	45	375	360
13	63	ASHD	110	105	50	50	330	330
14	50	ASHD	65	75	70	70	430	380
Mean ± SD	...	...	77 ± 16	74 ± 16	51 ± 11	51 ± 11	389 ± 39	374 ± 26
P value	...	...	*P* >0.1		...		*P* >0.1	

* These measurements were made in the control beats during atrial pacing at 80 to 90 beats/min.

A–H = interval from atrium to His bundle potential; ASHD = arteriosclerotic heart disease; DPH = diphenylhydantoin; H–V = interval from His bundle potential to onset of ventricular depolarization; *P* = probability; SD = standard deviation.

Methods

Studies were performed in 14 patients who were undergoing elective cardiac catheterization for evaluation of chest pain. No patient had clinically unstable angina or evidence of recent myocardial infarction. After informed consent was obtained, right heart catheterization was performed with the patients in the postabsorptive nonsedated state. No patient was receiving medications known to affect atrioventricular (A–V) conduction. Under local anesthesia induced by Xylocaine®, a bipolar or tripolar catheter was inserted percutaneously in the femoral vein and positioned in the region of the tricuspid valve for recording of His bundle electrograms.[13,14] A bipolar or quadripolar catheter was inserted in an antecubital vein and positioned against the wall of the right atrium for atrial pacing. Atrial pacing was accomplished with a Tektronics 2600 series pacemaker, using pulses of 2 msec duration at twice the diastolic threshold. The stimulator was connected to a battery-powered stimulus isolation box to prevent current leakage.

In each patient the conduction system was studied using the extrastimulus method.[10,11] With the atria driven at a basic drive rate of 80 to 90 beats/min, premature atrial impulses were introduced at intervals of 5 to 10 msec. The interval between the atrium and His spike (A–H time) was used as an approximation of A–V nodal conduction time. The interval between the His spike and onset of ventricular depolarization (H–V interval) was used as an approximation of His-Purkinje conduction time.

The atria were paced at a basic rate of 80 to 90 beats/min. After every 10th drive beat a premature beat (A_2) was introduced. The drive stimulus after the premature beat was then inhibited for 2,000 msec to facilitate measurement.

Determination of the refractory periods of the A–V conduction system was performed according to the method of Wit and Damato and co-workers.[10,11] The functional refractory period of the A–V node was defined as the minimal interval between two successive His bundle responses, both propagated from the atrium. The relative refractory period of the His-Purkinje system was defined as the H_1–H_2 interval at which H_2 conducted with an H_2–V_2 interval longer than the control beat or H_2 resulted in aberrant ventricular activation. The minimal H_1–H_2 interval not associated with His-Purkinje block was also recorded.

Pacing was performed in all patients until the premature stimulus did not conduct to the atrium. The refractory periods were determined at identical driving rates before and immediately after the intravenous administration of 5 mg/kg of diphenylhydantoin given at a rate of 50 mg/min.[7] All studies were completed within 10 minutes of the termination of drug administration. Recordings were made on an eight channel Electronics for Medicine recorder at paper speeds of 100 mm/sec.

Results

His bundle recording and refractory period determinations were made without difficulty in all patients. No episodes of bradycardia, A–V block or marked hypotension were associated with infusion of diphenylhydantoin. Four patients noted a mild sensation of dizziness immediately after the infusion, but the sensation subsided after 10 to 15 minutes and was not followed by neurologic sequelae.

A–V conduction: The A–H and H–V times at the control pacing rates of 80 to 90 beats/min before and after infusion of diphenylhydantoin are shown in Table I. No significant reduction was observed in the mean A–H interval after diphenylhydantoin. No changes were observed in the H–V interval in any of the patients studied. The functional refractory period of the A–V node was reduced from a control value of 389 ± 39 to 374 ± 26 msec (Table I). This change was not statistically significant ($P > 0.1$).

TABLE II

Effect of Diphenylhydantoin on His-Purkinje Conduction

Case no.	Minimal H_1-H_2 Interval Without His-Purkinje Block (msec)		Relative Refractory Period of His-Purkinje System (msec)		Aberrant Conduction		H–V Interval with His-Purkinje Block (msec)	After DPH (msec)
	Control	DPH	Control	DPH	Control	DPH		
1	430	355	420	350	RBBB	RBBB	40	40
2	425	395	420	390	LBBB	Decreased r in V_1	155	65
3	465	460	460	460 *	LBBB	Decreased r in V_1	80	55
4	420	395	418	<FRP	RBBB	0	50	50
5	355	330	350	<FRP	LBBB	0	85	55
6	425	375	420	<FRP	RBBB	0	73	50
7	430	370	420	<FRP	RBBB	0	85	75
8	410	395	400	<FRP	RBBB	0	45	45
9	415	375	410	370	RBBB	RBBB	50	50
10	450	420	440	<FRP	RBBB	0	35	35
11	430	410	425	<FRP	RBBB	0	45	45
12	430	395	420	385	RBBB	RBBB	45	45
13	380	330	370	<FRP	LBBB	0	50	50
14	425	380	420	<FRP	LBBB	0	150	70
Mean ± SD	421 ± 27	384 ± 34	...		...		70 ± 39	52 ± 11
P value	*P* <0.01		...		...		*P* >0.1	

DPH = diphenylhydantoin; FRP = functional refractory period of the A-V node, the minimal interval between two successive His bundle responses, both conducted from the atrium; LBBB and RBBB = left and right bundle branch block, respectively; *P* = probability; SD = standard deviation.

Intraventricular conduction: The results of His-Purkinje refractory period determinations before and after infusion of diphenylhydantoin are shown in Table II. Before the infusion nine patients manifested right bundle branch block aberration at a reproducible H_1–H_2 interval indicating the onset of the relative refractory period of the His-Purkinje system. The remaining five patients manifested left bundle branch block at a critical H_1–H_2 interval, and the disturbance was accompanied by an increase in H–V time in four. In all patients His-Purkinje conduction delay developed at all H_1–H_2 intervals below the relative refractory period of the His-Purkinje system.

After the administration of diphenylhydantoin, the relative refractory period of the His-Purkinje system was not measurable in 9 of the 14 patients (Table II), thus indicating that diphenylhydantoin had reduced the His-Purkinje relative refractory period to a value less than that of the minimal H_1–H_2 interval achieved (functional refractory period of the A–V node). In the remaining five patients, the relative refractory period of the His-Purkinje system was reduced (four patients) or the degree of aberrant conduction was altered (Case 3) by a reduction in H–V prolongation. The minimal H_1–H_2 interval without His-Purkinje conduction delay was reduced from a control value of 421 ± 27 to 384 ± 34 msec after administration of diphenylhydantoin. This change was statistically significant (P <0.01).

In all patients the administration of diphenylhydantoin altered the onset of aberrant conduction or the increase in H–V time, or both (Fig. 1). Diphenylhydantoin thus altered the conduction of premature beats in the His-Purkinje system in all 14 patients.

In one patient (Case 1) (Fig. 1) His-Purkinje block disappeared with decreasing A_1–A_2 intervals. The onset of His-Purkinje conduction delay occurred at an H_1–H_2 interval of 420 msec with an A_1–A_2 interval of 395 msec. At a shorter A_1–A_2 interval of 320 msec, the resulting H_1–H_2 interval of 430 msec exceeded the relative refractory period of the His-Purkinje system, and His-Purkinje delay was not produced. After infusion of diphenylhydantoin, the onset of His-Purkinje delay occurred at an H_1–H_2 interval of 350 msec. No H_1–H_2 intervals less than 350 msec were produced before atrial capture was lost.

Although the plasma levels of diphenylhydantoin were not measured in these patients, the dose used has been shown to result in initial therapeutic concentrations of 10 to 18 μg/ml when given at 5 minute intervals or as a 300 mg dose given over 1 to 3 minutes.[15] This method of administration has been shown to be effective in the treatment of clinical arrhythmias.[5] Previous reports suggest that the plasma concentration would be in the therapeutic range during the 10 minutes after drug administration.[15]

Discussion

Electrophysiologic effects: The electrophysiologic effects of diphenylhydantoin have been studied in both the isolated Purkinje fiber and the intact heart.[7–9,16,17] In the perfused canine Purkinje fiber

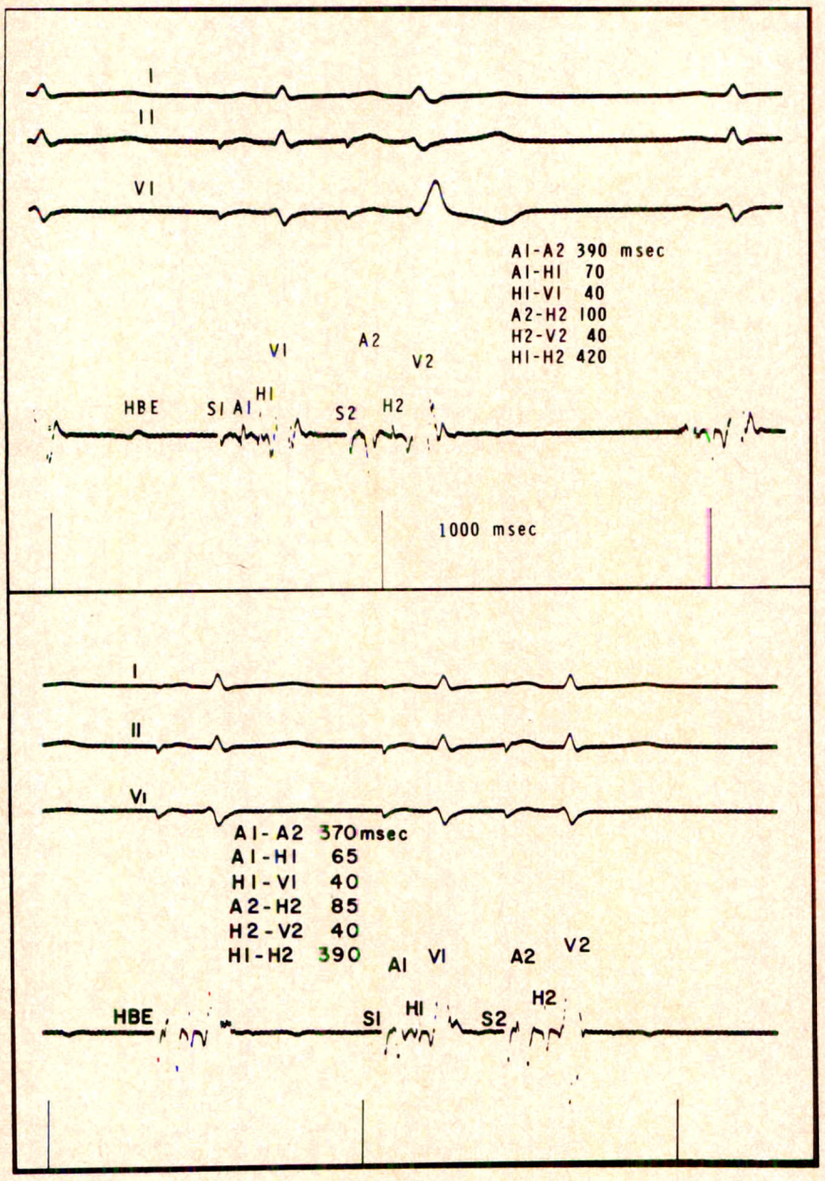

FIGURE 1. Case 1. His bundle electrograms. The basic pacing rate is 84 beats/min; the time lines are at 1,000 msec intervals. The recordings made before infusion of diphenylhydantoin **(top panel)** show the development of right bundle branch block and the shift of the QRS axis toward the left at an H_1–H_2 interval of 420 msec. All H_1–H_2 intervals less than 420 msec were associated with right bundle branch block. After administration of diphenylhydantoin **(bottom panel)** conduction is normal at an H_1–H_2 interval of 390 msec. Even when the H_1–H_2 interval was reduced, diphenylhydantoin inhibited the appearance of right bundle branch block by altering the relative refractory period of the His-Purkinje system.

diphenylhydantoin caused a decrease in the slope of phase 4 depolarization resulting in a decrease in automaticity.[17] In addition, diphenylhydantoin alters the time course of the transmembrane action potential by reducing all phases of repolarization. The time course of recovery of repolarization shortens more than that of the recovery of excitability; this effect may act to reduce decremental conduction and alter the appearance of aberrant conduction.

The effect of diphenylhydantoin in the intact heart has also been studied extensively. The P–R and A–H intervals have been reduced when compared during rapid atrial pacing in both human subjects[7–9] and experimental animals.[16] However, when diphenylhydantoin was tested in three animals with chronic cardiac denervation, depression of sinus rate and prolongation of A–V conduction was observed.[16] These findings suggest that diphenylhydantoin may act in part through an anticholinergic effect. Additional studies have shown that diphenylhydantoin inhibits the action of acetylcholine on the myoneural junction.[18] Bradycardia and increased A–V block have been observed[19,20] in patients who died after intravenous administration of diphenylhydantoin. In the experimental animal, the decrease in A–V conduction time produced by diphenylhydantoin was significantly greater in the digitalized animals.[8] Diphenylhydantoin has also been effective clinically in treating both supraventricular and ventricular arrhythmias produced by digitalis.[4–6]

Effects on intraventricular conduction defects: The effect of diphenylhydantoin on intraventricular conduction has been recently studied. Measurements of the total H–V time during atrial pacing have shown no change after intravenous administration of diphenylhydantoin in human subjects.[7–9] Similar

findings have been reported in the intact dog heart.[16] In contrast, Haiat et al.[21] recently reported a case of right bundle branch block and left posterior hemiblock associated with atrial tachycardia. The intravenous administration of 250 mg of diphenylhydantoin restored normal intraventricular conduction. The normalization of intraventricular conduction was not rate-related since the conduction disturbances were previously observed at a slower ventricular rate. The results obtained in the patients described here are consistent with the loss of intraventricular conduction defects after intravenous diphenylhydantoin. Diphenylhydantoin produced a significant decrease in the minimal H_1–H_2 interval achieved without His-Purkinje delay and altered the conduction of premature beats in the His-Purkinje system in all 14 patients.

Our results demonstrate only a qualitative effect of diphenylhydantoin on the His-Purkinje system. Additional studies are needed to correlate the effects of diphenylhydantoin in the normal and abnormal heart with changes in serum and tissue levels. Our data do show that the administration of diphenylhydantoin alters intraventricular conduction by decreasing the relative refractory period of the His-Purkinje system or shortening the H–V prolongation associated with aberrant conduction, or both. In contrast to previous findings,[7–9] they indicate that diphenylhydantoin has a significant effect on intraventricular conduction in man.

Between the publication of these findings in part in abstract form[12] and the submission of this manuscript, Damato et al.[22] reported significant changes in His-Purkinje conduction after administration of diphenylhydantoin.[22] As in our study, no significant changes were observed in the functional refractory period of the A–V node. Our report confirms their results and provides specific examples of the effect of diphenylhydantoin on left and right bundle branch aberration in man.

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Effect of Glucose-Insulin-Potassium Infusion on the Human Conduction System

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His bundle electrograms were performed in 21 patients with organic heart disease. Recordings were made at various rates utilizing right atrial pacing. A mixture containing 50 g of glucose, 10 mEq of potassium and 20 units of insulin was given intravenously over 10 minutes to 10 subjects. The P–A, A–H, H–Q and H–S intervals were determined before and immediately after the glucose-insulin-potassium infusion. A significant prolongation in the A–H interval occurred with negligible effects on the P–A, H–Q and H–S intervals. At the atrial pacing rate of 100/min, the average A–H interval increased from the control value of 140 msec to 151 msec after the infusion ($P < 0.05$); at the pacing rate of 140/min, the A–H interval increased from 145 to 165 msec ($P < 0.05$). The identical study was performed in three additional patients who received an infusion of 50 g of glucose and 20 units of insulin. No significant change was observed in the conduction system. In eight patients a solution of 2.6 mEq of potassium in 65 cc of 5 percent glucose and water was infused over an 8 minute period. A significant prolongation of the A–H interval was observed. At the atrial pacing rate of 100/min, the average A–H interval increased from the control value of 122 to 133 msec after the glucose and potassium infusion ($P < 0.05$), whereas at the pacing rate of 140/min, the A–H interval increased from 165 to 188 msec ($P < 0.05$). These findings demonstrate that the potassium in a glucose-potassium-insulin infusion may cause impaired conduction through the atrioventricular node.

In 1962 Sodi-Pallares et al.[1] reported that intravenous infusion of a potassium-glucose-insulin solution can normalize the electrocardiographic signs of myocardial infarction. These workers also stressed the usefulness of this solution in reducing the incidence of cardiac arrhythmias. The Medical Research Council working party questioned the validity of these observations.[2] Recently, two groups of workers[3,4] documented that glucose-insulin-potassium infusions are a useful adjunct to the management of severe congestive heart failure. When Maroko et al.[5] observed that such infusions can reduce the extent of myocardial necrosis in dogs after coronary arterial occlusion, renewed interest in this form of therapy quickly followed.

The effects of this solution on the human conduction system are unknown. We therefore administered glucose, potassium and insulin to 10 patients with cardiac disease, and a solution of glucose and potassium to an additional 8 patients. Electrocardiograms and bundle of His electrograms were recorded before and after the infusions, and the effects on atrioventricular and intraventricular conduction were determined.

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TABLE I

Clinical Data in 21 Cases

Case no.	Age (yr) & Sex	Electrocardiographic Findings	Diagnosis
1	80F	Sinus bradycardia	Arteriosclerotic heart disease
2	62F	Left ventricular hypertrophy	Hypertension
3	78M	Right bundle branch block	Cor pulmonale
4	78M	Recent anterior wall myocardial infarction	Arteriosclerotic heart disease
5	79F	Nonspecific ST–T wave changes	Arteriosclerotic heart disease
6	57F	P mitrale	Rheumatic heart disease
7	70M	1st degree A–V block	Arteriosclerotic heart disease
8	78M	Nonspecific ST–T wave changes	Arteriosclerotic heart disease
9	42F	Recent anterior wall myocardial infarction	Arteriosclerotic heart disease
10	66M	Sinus bradycardia	Primary myocardial disease
11	55M	Recent anterior wall myocardial infarction	Arteriosclerotic heart disease
12	58M	Left ventricular hypertrophy	Arteriosclerotic heart disease
13	25F	Right bundle branch block	Rheumatic heart disease
14	67F	Sinus bradycardia	Bradycardia-tachycardia syndrome
15	73M	Recent inferior wall myocardial infarction	Arteriosclerotic heart disease
16	68M	Left bundle branch block	Arteriosclerotic heart disease
17	78F	Nonspecific ST–T wave changes	Arteriosclerotic heart disease
18	19F	Left ventricular hypertrophy	Idiopathic hypertrophic subaortic stenosis
19	72M	Left anterior hemiblock	Bradycardia-tachycardia syndrome
20	42M	Normal	Syncope (origin unknown)
21	24F	Nonspecific ST–T wave changes	Sarcoidosis

Material and Methods

The study group consisted of 21 patients with organic heart disease. The clinical features of the group are summarized in Tables I and II. All patients were informed of the nature of the study and gave signed consent. They were studied in the supine position in a postabsorptive, nonsedated state.

With use of local anesthesia, a bipolar pacing catheter was introduced percutaneously into the right femoral vein and fluoroscopically positioned at the tricuspid valve. The position was adjusted to obtain optimal recordings of the bundle of His electrogram. The proximal terminals of the catheter were attached to an electrocardiographic amplifier, and the bipolar His electrogram was recorded at a frequency setting of 40 to 500 cycles/sec on a DR-12 Electronics for Medicine recorder at paper speeds of 100 mm/sec. A no. 6F bipolar catheter was passed by way of the right antecubital vein and positioned along the lateral wall of the right atrium. The proximal terminals of the electrodes were connected to a battery-powered Medtronic pacemaker (model 5837). The milliamperage was adjusted to twice threshold to assure reliable atrial capture. A simultaneous surface electrocardiographic lead was also recorded. All electrical equipment was carefully grounded. Measurements, in milliseconds, were made of the following intervals:

1. *The P–A interval:* the interval from onset of the P wave during normal sinus conduction recorded on the standard electrocardiographic lead to the first rapid deflection of the A wave on the bipolar electrogram. The P–A time represents intraatrial conduction time. The normal value is 27 ± 18 msec.[6] During atrial pacing the P–A time is measured from the pacing impulse to A.

TABLE II

Serum Electrolytes at Time of Study

Case no.	Na (mEq/liter)	K (mEq/liter)	Cl (mEq/liter)	CO_2 (mEq/liter)	BUN (mg/100 ml)
1	137	4.1	98	30	16
2	...	...	...	...	14
3	138	3.9	98	27	32
4	137	4.4	95	28	32
5	141	3.8	97	35	22
6	...	...	...	...	11
7	133	4.4	100	27	17
8	141	4.4	104	23	14
9	143	5.0	100	30	21
10	140	5.2	110	21	19
11	134	4.7	97	21	33
12	136	4.6	99	25	13
13	139	3.7	111	26	20
14	142	3.9	97	36	15
15	133	5.5	95	27	29
16	135	4.5	100	22	18
17	141	4.0	102	27	24
18	140	4.7	103	30	8
19	137	4.5	97	29	17
20	130	4.1	99	23	14
21	139	4.5	94	34	14

BUN = blood urea nitrogen; Cl = chloride; CO_2 = carbon dioxide; K = potassium; Na = sodium.

TABLE III

Measurements of Atrioventricular and Intraventricular Conduction (in msec) in 10 Patients Before and After Glucose-Potassium-Insulin Infusion*

Control Data						Data After Infusion					
HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time	HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time
					Case 1						
50	20	80	40	120	...	54	20	80	40	120	...
80	40	90	40	120	...	80	40	90	40	120	...
90	40	95	40	120	...	90	40	100	40	120	...
100	40	100	40	120	...	100	40	120	40	120	...
110	40	110	40	120	...	110	40	140	40	120	...
120	40	140	40	120	...	120	40	160	40	120	...
130	40	160	40	120	...	130	40	210	40	120	...
140	40	170	40	120	...	140	40	220	40	120	...
150	40	180	40	120	5400	150	Wenckebach		40	120	...
					Case 2						
63	40	120	40	140	...	65	40	120	40	140	...
80	60	140	40	140	...	80	60	140	40	140	...
90	60	150	40	140	...	90	60	150	40	140	...
100	60	160	40	140	...	100	60	160	40	140	...
110	60	180	40	140	...	110	60	180	40	140	...
120	60	200	40	140	...	120	60	220	40	140	...
130	60	220	40	140	...	130	Wenckebach		40	140	...
140	Wenckebach		40	140	1500						1280
					Case 3						
94	50	270	80	210	...	88	50	280	80	210	...
100	70	270	80	210	...	100	70	280	80	210	...
110	70	310	80	210	...	110	70	320	80	210	...
120	Wenckebach		80	210	940	120	Wenckebach		80	210	1060
					Case 4						
88	30	70	55	155	...	94	20	75	55	155	...
100	50	70	55	155	...	100	40	75	55	155	...
110	50	80	55	155	...	110	40	100	55	155	...
120	50	90	55	155	...	120	40	105	55	155	...
130	50	90	55	155	...	130	40	105	55	155	...
140	50	100	55	155	...	140	40	110	55	155	...
150	50	100	55	155	800	150	40	120	55	155	800
					Case 5						
75	40	80	60	140	...	70	40	80	70	150	...
90	80	100	60	140	...	90	110	110	70	150	...
100	80	110	60	140	...	100	110	130	70	150	...
110	80	130	60	140	...	110	110	150	70	150	...
120	80	190	60	140	...	120	110	190	70	150	...
130	Wenckebach		60	140	740	130	Wenckebach		70	150	840
					Case 6						
70	40	100	40	120	...	75	40	100	40	120	...
90	40	160	40	120	...	90	40	160	40	120	...
100	40	160	40	120	...	100	40	185	40	120	...
110	40	170	40	120	...	110	40	185	40	120	...
120	40	190	40	120	...	120	40	195	40	120	...
130	40	195	40	120	...	130	40	210	40	120	...
140	40	200	40	120	...	140	40	220	40	120	...
150	40	210	40	120	880	150	40	265	40	120	...

TABLE III continued

Control Data						Data After Infusion					
HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time	HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time
					Case 7						
81	20	160	40	140	...	86	20	180	40	140	...
90	50	170	40	140	...	90	50	180	40	140	...
100	50	170	40	140	...	100	50	190	40	140	...
110	50	210	40	140	...	110	50	250	40	140	...
120	50	250	40	140	...	120	50	330	40	140	...
130	50	330	40	140	...	130	50	430	40	140	...
140	50	360	40	140	...	140	Wenckebach		40	140	...
150	Wenckebach		40	140	720	150					860
					Case 8						
73	20	100	40	120	...	75	20	100	40	120	
90	40	100	40	120	...	90	40	100	40	120	...
100	40	100	40	120	...	100	40	110	40	120	...
110	40	110	40	120	...	110	40	120	40	120	...
120	40	120	40	120	...	120	40	140	40	120	...
130	40	120	40	120	...	130	40	150	40	120	...
140	40	140	40	120	...	140	40	160	40	120	...
150	40	160	40	120	900	150	40	190	40	120	920
					Case 9						
120	20	60	40	140	...	120	20	60	40	140	...
130	20	90	45	145	...	...	...	...	...	...	...
140	20	100	45	145	...	140	20	120	45	145	...
150	20	110	45	145	580	150	20	120	45	145	600
					Case 10						
68	40	100	40	140	...	57	40	100	50	150	...
90	40	110	40	140	...	90	40	110	50	150	...
100	40	120	40	140	...	100	40	120	50	150	...
110	40	130	40	140	...	110	40	130	50	150	...
120	40	150	40	140	...	120	40	150	50	150	...
130	40	160	40	140	...	130	40	160	50	150	...
140	40	160	40	140	...	140	40	160	50	150	...
150	40	180	40	140	1140	150	40	180	50	150	1300

*Conduction values at the slowest heart rate in each patient were obtained without pacing.
HR = heart rate (beats/min).

2. *A–H interval:* the interval from the first rapid deflection of the A wave to the first rapid deflection of the bundle of His electrogram. The A–H time represents conduction time through the atrioventricular (A–V) node. The normal value is 92 ± 38 msec.[6]

3. *H–Q interval:* the interval from the first rapid bundle of His deflection to the onset of the QRS deflection in the electrocardiogram. The H–Q interval approximates conduction time in the specialized tissues of the His-Purkinje system. The normal value is 43 ± 12 msec.[6]

4. *H–S interval:* the interval from the first rapid bundle of His deflection to the end of the QRS deflection on the electrocardiogram. The H–S interval approximates total intraventricular conduction time.

The P–A, A–H, H–Q and H–S intervals were recorded before atrial pacing and at atrial pacing rates of 80 to 150 beats/min. In 10 patients a solution containing 50 g of glucose, 10 mEq of potassium and 20 units of insulin was then infused intravenously over 10 minutes and the various intervals were recorded, without atrial pacing, immediately after the infusion. Atrial pacing was then performed with simultaneous recording of the His bundle electrogram. In addition, the recovery time of the sinus nodal pacemaker, after sudden cessation of the highest pacing rate obtained, was observed before and after the infusion. The identical studies were performed in three additional patients who received a solution containing 50 g of glucose and 20 units of insulin but no potassium. In a third study, performed in the identical manner, 8 additional patients received an infusion of 2.6 mEq of potassium in 65 cc of 5 percent glucose and water. This solution was infused over 8 minutes.

Results

Glucose-potassium-insulin solution: Table III shows the measurements of the P–A, A–H, H–Q and H–S intervals in the 10 patients before and after

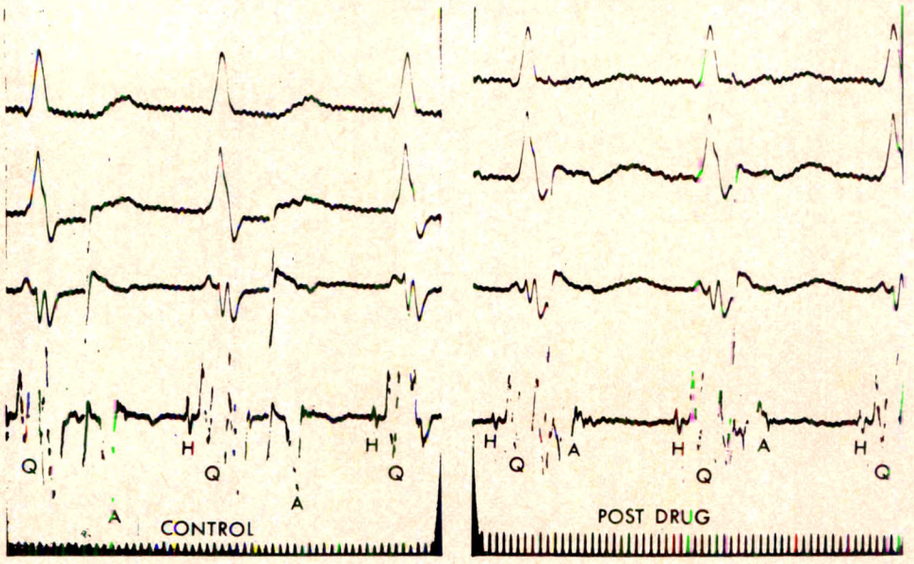

FIGURE 1. Case 7. His bundle electrogram obtained before and immediately after the glucose-potassium-insulin infusion. The right atrial pacing rate is 120 beats/min. The A–H interval in the control period is 250 msec and after the infusion it increases to 330 msec. Time lines are 0.02 second apart.

infusion of the glucose-potassium-insulin solution. The infusion had no significant effect on the P–A, H–Q or H–S intervals. However, at the atrial pacing rate of 100 beats/min, the average A–H interval increased from a control value of 140 msec to 151 msec after the infusion ($P < 0.05$). At the atrial pacing rate of 140 beats/min, the A–H interval increased from 145 to 165 msec ($P < 0.05$). Figure 1 shows a representative recording. Second degree heart block occurred at lower pacing rates in three subjects after administration of glucose-potassium-insulin than before the infusion. The postsuppression sinoatrial recovery time was increased in six of eight patients after infusion. The average recovery time control value of 915 msec increased to 958 msec after the infusion. This change was not significant.

Insulin-glucose solution: No significant change was observed in any of the intervals in the three patients who received the insulin-glucose solution (Table IV).

Glucose-potassium solution: The infusion of potassium in 5 percent glucose and water had no significant effect on the P–A, H–Q or H–S intervals in the eight patients to whom it was administered (Table V). At the atrial pacing rate of 100 beats/min, the average A–H interval increased from 122 to 133 msec ($P < 0.05$). At the atrial pacing rate of 120 beats/min, the A–H interval increased from 136 to 148 msec ($P < 0.02$); at the pacing rate of 140 beats/min, the A–H interval increased from 165 to 188 msec ($P < 0.05$). Figure 2 shows a typical recording. Second degree heart block occurred at lower pacing rates in five patients after the glucose-potassium infusion than before the infusion. The postsuppression sinoatrial recovery time was increased in five of eight patients after the infusion.

Discussion

The glucose-potassium-insulin infusion produced in patients with cardiac disease a significant increase

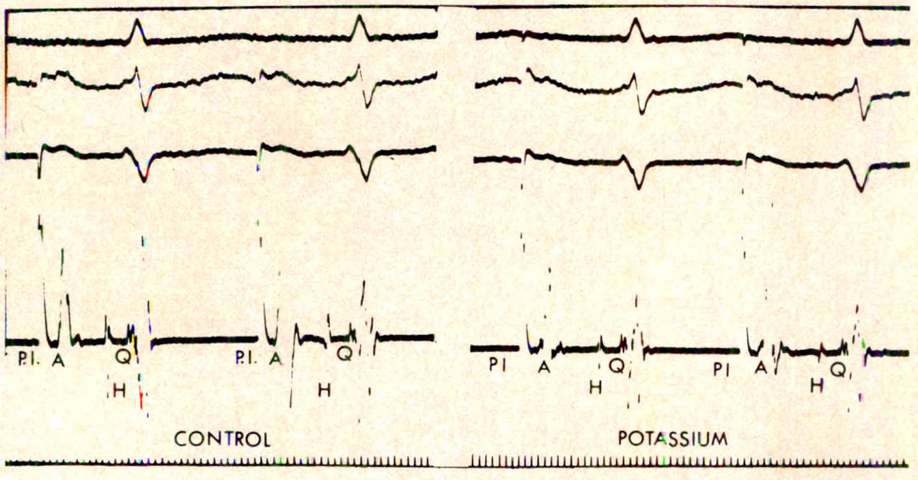

FIGURE 2. Case 19. His bundle electrogram obtained before and immediately after the glucose-potassium infusion. The right atrial pacing rate is 90 beats/min. The A–H interval in the control period is 140 msec and after the infusion it increases to 170 msec. Time lines are 0.02 second apart. P.I. = pacing impulse.

TABLE IV

Measurements of Atrioventricular and Intraventricular Conduction (in msec) In Three Patients Before and After Glucose-Insulin Infusion*

Control Data						Data After Infusion					
HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time	HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time
					Case 11						
103	20	100	70	190	...	103	20	100	70	190	...
110	40	100	70	190	...	110	40	100	70	190	...
120	40	110	70	190	...	120	40	100	70	190	...
130	40	110	70	190	...	130	40	110	70	190	...
140	40	150	70	190	...	140	40	150	70	190	...
150	40	160	70	190	660	150	40	160	70	190	640
					Case 12						
70	40	80	60	140	...	75	40	80	60	140	...
90	80	90	60	140	...	90	80	90	60	140	...
100	80	100	60	140	...	100	80	100	60	140	...
110	80	110	60	140	...	110	80	110	60	140	...
120	80	120	60	140	...	120	80	120	60	140	...
130	80	130	60	140	...	130	80	130	60	140	...
140	80	140	60	140	...	140	80	140	60	140	...
150	80	150	60	140	1060	150	80	150	60	140	1040
					Case 13						
73	20	100	50	170	...	84	20	100	50	170	...
100	20	100	50	170	...	100	20	100	50	170	...
110	20	110	50	170	...	110	20	110	50	170	...
120	20	120	50	170	...	120	20	120	50	170	...
130	20	120	50	170	...	130	20	120	50	170	...
140	20	130	50	170	...	140	20	130	50	170	...
150	20	140	50	170	780	150	20	140	50	170	720

*The conduction values at slowest heart rate in each patient were obtained without pacing.
HR = heart rate (beats/min).

in the A–H interval but had only minimal effects on the P–A, H–Q and H–S intervals. This represents a delay in conduction through the A–V node. Second degree heart block occurred in three subjects at lower pacing rates after the glucose-potassium-insulin infusion than before the infusion. The postsuppression sinoatrial recovery time was increased in most cases after the infusion.

The infusion of a solution containing only glucose and insulin had no significant effect on the conduction system, thus suggesting that potassium played a major role in the impaired conduction in the A–V node. When the infusion of glucose and potassium also produced a significant increase in the A–H interval, this finding confirmed that potassium was indeed the agent responsible for the impaired conduction in the A–V node.

Sodi-Pallares et al.[1] were the first to popularize use of the polarizing solution in patients with cardiac disease. They observed that the combined metabolic activity of insulin and glucose can accelerate the movement of potassium into the myocardial cell. The potassium may even be preferentially picked up by injured myocardium, which is more deficient in this cation than normal tissue. Such an ionic shift has been thought to stabilize the electrical state of the myocardial cell and thus reduce myocardial irritability and arrhythmias by restoring normal polarity. However, Surawicz[7] in his extensive review of the subject observed that the two important assumptions underlying the theoretical basis of treatment with polarizing solutions remain unproved. There is no evidence that the ischemic area contains fibers that have lost only a portion of their potassium and there is no evidence that in such fibers the administration of a glucose-insulin-potassium solution restores the concentration of potassium to normal.

Most clinical studies have shown that the frequency of arrhythmias in patients with myocardial infarction is not reduced with the administration of potassium, glucose and insulin[2,8,9]; however, some workers have reported a decreased frequency of arrhythmias.[1,10] Mittra[11] reported that an infusion of glucose, potassium and insulin can decrease atrioventricular block complicating myocardial infarction; however, the solution was given only to patients with

TABLE V

Measurements of Atrioventricular and Intraventricular Conduction (in msec) In Eight Patients Before and After Glucose-Potassium Infusion*

Control Data						Data After Infusion					
HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time	HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time
					Case 14						
63	40	125	60	165	...	63	45	135	60	165	...
80	40	145	60	165	...	80	105	145	60	165	...
90	40	155	60	165	...	90	110	155	60	165	...
100	40	160	60	165	...	100	120	165	60	165	...
110	40	180	60	165	...	110	120	195	60	165	...
120	40	210	60	165	...	120	Wenckebach		60	165	...
130	40	280	60	165	...	...	...	...	...	...	...
140	Wenckebach		60	165	1050	...	...	...	...	...	1340
					Case 15						
75	40	110	40	160	...	78	40	120	40	160	...
80	45	120	40	160	...	80	55	120	40	160	...
90	45	120	40	160	...	90	55	130	40	160	...
100	45	140	40	160	...	100	55	140	40	160	...
110	45	140	40	160	...	110	55	155	40	160	...
120	45	150	40	160	...	120	55	160	40	160	...
130	45	155	40	160	...	130	Wenckebach		40	160	...
140	45	175	40	160	...	...	...	...	...	...	...
150	Wenckebach		40	160	550	...	...	...	...	...	760
					Case 16						
65	35	120	40	160	...	58	35	130	40	160	...
100	60	130	40	160	...	100	60	140	40	160	...
110	60	140	40	160	...	110	60	150	40	160	...
120	60	160	40	160	...	120	60	180	40	160	...
130	60	200	40	160	...	130	Wenckebach		40	160	...
140	Wenckebach		40	160	1160	...	...	...	...	...	1160
					Case 17						
81	20	90	45	145	...	81	20	100	45	145	...
100	20	90	45	145	...	100	30	110	45	145	...
110	20	110	45	145	...	110	30	120	45	145	...
120	20	120	45	145	...	120	30	130	45	145	...
130	20	130	45	145	...	130	30	150	45	145	...
140	20	140	45	145	...	140	30	160	45	145	...
150	20	150	45	145	1020	150	30	170	45	145	740
					Case 18						
75	20	70	35	115	...	91	20	80	35	115	...
100	20	90	35	115	...	100	20	100	35	115	...
110	20	110	35	115	...	110	20	110	35	115	...
120	20	110	35	115	...	120	20	110	35	115	...
130	20	130	35	115	...	130	20	130	35	115	...
140	20	140	35	115	...	140	20	140	35	115	...
150	20	220	35	115	660	150	Wenckebach		35	115	1000
					Case 19						
68	55	100	60	160	...	63	60	120	60	160	...
90	60	140	60	160	...	90	70	170	60	160	...
100	60	190	60	160	...	100	Wenckebach		60	160	...
110	60	240	60	160	...	...	...	...	...	...	...
120	Wenckebach		60	160	1140	...	...	...	...	...	1140

TABLE V continued

Control Data						Data After Infusion					
HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time	HR	P–A or PI–A	A–H	H–Q	H–S	Recovery Time
					Case 20						
58	20	100	50	130	...	60	20	100	50	130	...
100	40	120	50	130	...	100	40	140	50	130	...
110	40	160	50	130	...	110	40	160	50	130	...
120	40	165	50	130	...	120	40	180	50	130	...
130	40	210	50	130	...	130	40	220	50	130	...
140	40	260	50	130	...	140	40	300	50	130	...
150	Wenckebach		50	130	960	150	Wenckebach		50	130	1160
					Case 21						
94	20	60	40	120	...	91	20	60	40	120	...
110	30	100	40	120	...	110	30	130	40	120	...
120	30	110	40	120	...	120	30	130	40	120	...
130	30	120	40	120	...	130	30	140	40	120	...
140	30	120	40	120	...	140	30	150	40	120	...
150	30	130	40	120	740	150	30	150	40	120	940

*Conduction values at the slowest heart rate in each patient were obtained without pacing.
HR = heart rate (beats/min).

an inferior wall myocardial infarction, and normal conduction did not return for many hours. It is now recognized that spontaneous restoration of sinus rhythm is the rule in patients with inferior wall myocardial infarction complicated by various degrees of A–V block.

Effects of potassium on A–V conduction: Potassium can have profound effects on A–V conduction. Intravenous administration of potassium in the dog has a biphasic effect on A–V conduction. Initially, mild hyperkalemia accelerates A–V conduction by anticholinergic effects and a direct effect upon the action potential of the conduction fibers. Subsequently, continued elevation of potassium levels depresses A–V conduction by a potentiation of vagal effects and a reduction of the resting potential and the rate of rise of phase 0 of the action potential.[12] Electrophysiologic studies of the A–V junction indicate that the depression of conduction by potassium occurs largely at the atrionodal, nodal–His, or His–Purkinje regions and that the true nodal or N region is quite resistant to the depressing effect of potassium.[13,14]

Plasma potassium concentration is only one of several factors that determine the effect of potassium on A–V conduction. Individual variations in response to the same change of plasma potassium concentration may be caused by organic diseases of the conducting system or by physiologic factors, such as the complex interplay between potassium and acetylcholine.[15] Indeed, Patient 7 in our study had first degree A–V block due to a prolongation of the A–H interval. With the administration of the glucose-potassium-insulin solution a 100 msec prolongation in the A–H interval occurred at the atrial pacing rate of 130 beats/min. This suggests that a glucose-potassium-insulin infusion can prolong conduction time to an alarming degree in patients with depressed A–V conduction.

Another important factor is the rate of change of plasma potassium concentration. A rapid change in the plasma potassium concentration may have a different effect than a slow change on the electrophysiologic properties of cardiac fibers.[16] A rapid change from a low to normal potassium concentration may depress pacemaker activity.[17] One can produce or abolish at will the A–V block in patients and in dogs by slight but rapid changes of the rate of potassium administration.[18] When potassium is administered rapidly, complete A–V block may occur, even in the absence of a measurable rise in plasma potassium concentration.[19]

The antiarrhythmic effect of potassium is attributed to a slowing of the diastolic depolarization of the pacemaker fibers. It is also probable that by affecting conduction, potassium eliminates ectopic rhythms caused by reentry.[20]

Burchell[21] has recently postulated that more lives may have been lost than saved by potassium therapy in the past year in American hospitals. There are no statistics to support or negate this hypothesis. However, our study throws new light on the potential hazards of a potassium infusion. Small amounts of infused potassium can impair cardiac conduction. Undoubtedly larger amounts of potassium, particularly when infused, can cause even more profound alterations in cardiac conduction. Thus, in certain clinical settings the administration of potassium may prove fatal.

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Effect of Glucagon on Cardiac Conduction in Man

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His bundle electrograms were obtained in 26 patients before and after intravenous administration of glucagon (50 μg/kg). The group consisted of 4 patients with normal conduction and 22 patients with conduction disease. The P–A interval, measured in all patients, was 35 ± 1.4 msec (mean ± standard error of the mean) before and 30 ± 1.5 msec after infusion of glucagon ($P < 0.001$). The mean A–H interval during sinus rhythm in all patients and during pacing at 100/min in 21 patients was, respectively, 97 ± 6.0 msec and 114 ± 6.4 msec before, and 96 ± 6.0 msec and 114 ± 6.6 msec after infusion of glucagon (not significant). The mean H–V interval in 25 patients was 48 ± 2.6 msec before and 49 ± 2.0 msec after infusion of glucagon (not significant). The mean sinus rate and sinus recovery times were, respectively, 73 ± 3.0 beats/min and 1,025 ± 42.0 msec before and 81 ± 3.0 beats/min and 919 ± 27.0 msec after infusion of glucagon ($P < 0.001$ and < 0.01). Functional and effective refractory periods were measured (in milliseconds) with use of the atrial extrastimulus technique. The mean atrial functional and effective refractory periods (21 patients) were, respectively, 273 ± 11.6 and 252 ± 12.0 before and 256 ± 10.0 and 238 ± 9.6 after infusion of glucagon ($P < 0.001$ and < 0.01). Mean atrioventricular (A–V) nodal functional refractory period (22 patients) and effective refractory period (15 patients) were 465 ± 22.0 and 404 ± 33.0 before and 457 ± 23.0 and 395 ± 32.0 after the infusion (not significant). The mean effective refractory period of the His-Purkinje system (2 patients) was 440 ± 45.0 before and 425 ± 55.0 after infusion of glucagon (not significant).

In summary, glucagon increased sinus nodal automaticity, as manifested by an increase in sinus rate and decrease of sinus nodal recovery time, and improved intraatrial conduction as manifested by a reduction of the P–A interval and atrial functional and effective refractory periods. Glucagon had no effect on A–V nodal or intraventricular conduction.

Glucagon, which has both positive inotropic and chronotropic actions, has been recommended for management of intractable congestive heart failure and cardiogenic shock.[1–9] Canine studies have demonstrated that this agent also facilitates atrioventricular (A–V) nodal conduction.[10–12] This latter action has been cited as potentially advantageous, particularly in patients with conduction disease. However, human studies concerning the effects of glucagon on cardiac conduction have been limited.[13]

In the present study we used His bundle recording and cardiac pacing to examine systematically the effects of glucagon on cardiac conduction in man. Conduction intervals as well as refractory periods were measured. Our results confirm the positive chronotropic effect of glucagon on the sinus node, as manifested by increase in sinus rate and shortening of sinoatrial (S–A) nodal recovery time. In addition,

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TABLE I

Summary of Electrophysiologic Findings After Administration of Glucagon

	Patients (no.)	State	Mean ± SEM	P Value
Sinus rate (beats/min)	26	C	73 ± 3.0	<0.001
		G	81 ± 3.0	
SRT (msec)	26	C	1025 ± 42.0	<0.01
		G	919 ± 27.0	
P–A interval (msec)	26	C	35 ± 1.4	<0.001
		G	30 ± 1.5	
A–H interval (NSR) (msec)	26	C	97 ± 6.0	NS
		G	96 ± 6.0	
A–H interval (at HR 100/min) (msec)	21	C	114 ± 6.4	NS
		G	114 ± 6.6	
H–V interval (msec)	25	C	48 ± 2.6	NS
		G	49 ± 2.0	
HR during Wenckebach periods (beats/min)	21	C	144 ± 6.0	<0.05
		G	149 ± 6.0	
Atrial FRP (msec)	21	C	273 ± 11.6	<0.001
		G	256 ± 10.0	
Atrial ERP (msec)	21	C	252 ± 12.0	<0.01
		G	238 ± 9.6	
A–V nodal FRP (msec)	22	C	465 ± 22.0	NS
		G	457 ± 23.0	
A–V nodal ERP (msec)	15	C	404 ± 33.0	NS
		G	395 ± 32.0	
VSCS ERP (msec)	2	C	440 ± 45.0	NS
		G	425 ± 55.0	

A–V = atrioventricular; C = control; ERP = effective refractory period; FRP = functional refractory period; G = glucagon; HR = heart rate; NS = not significant; NSR = normal sinus rhythm; SEM = standard error of the mean; SRT = sinus nodal recovery time; VSCS = ventricular specialized conduction system.

glucagon facilitated intraatrial conduction as manifested by a shortening of both the P–A interval and atrial refractory periods. Glucagon had no significant effect on A–V nodal or intraventricular conduction.

Methods

The study group consisted of 26 patients with heart disease undergoing diagnostic cardiac catheterization or electrophysiologic studies. Four had normal conduction, 21 had first degree A–V block or bundle branch block, or both, and 1 had complete heart block. Informed consent was obtained.

His bundle electrograms were recorded using a tripolar catheter passed by way of the femoral vein.[14,15] A quadripolar catheter was passed to the high right atrium for atrial pacing (2 poles) and for recording high right atrial electrograms (2 poles). Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-16, Electronics for Medicine) at paper speeds of 100 and 200 mm/sec. Simultaneous electrocardiographic leads I, II, III and V_1 were recorded.

Atrial pacing was performed at increasing rates in increments of 10 beats/min until Wenckebach periods were observed. Sinus nodal recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at a rate of 130/min.[15] Effective and functional refractory periods of the atrium, A–V node and His-Purkinje system were measured with the extrastimulus technique as described by Wit et al.[16] A cycle length approximately 10 to 20 percent faster than the sinus rate was utilized so that refractory periods could be measured at identical cycle lengths before and after administration of glucagon.

The following intervals were measured in milliseconds[15,17]*:*

1. P–A (normal 9 to 45 msec): The interval from the onset of the P wave to the first rapid deflection of the low right atrial electrogram recorded from the His bundle catheter, reflecting conduction time from the high to the low right atrium. If the onset of the P wave could not be well delineated, the onset of the high right atrial electrogram was utilized. This was measured in all patients.

2. A–H (normal 54 to 130 msec): The interval from the onset of the low right atrial electrogram to the first high frequency component of the His bundle electrogram, reflecting A–V nodal conduction time. This interval was measured during sinus rhythm and at equivalent paced rates before and after administration of glucagon.

3. H–V (normal 31 to 55 msec): From the first high frequency component of the His bundle electrogram to the earliest QRS deflection on the surface electrocardiogram. This interval reflects conduction time in the His-Purkinje system. It could not be measured in the patient with complete heart block, since it was distal to the H potential.

For each of these intervals, 10 beats were averaged before and after infusion of glucagon, and the mean values were used for comparison.

The following definitions were used in regard to refractory periods: A_1, H_1 and V_1 were the atrial, His bundle and ventricular electrograms of driven beats (S_1). A_2, H_2 and V_2 were the atrial, His bundle and ventricular electrograms in response to the extrastimulus (S_2). The atrial effective refractory period was the longest S_1–S_2 interval at which S_2 did not result in atrial capture. The atrial functional refractory period was the shortest attainable propagated A_1–A_2 interval. The A–V nodal effective refractory period was the longest A_1–A_2 interval at which conduction failed to the His bundle. The A–V nodal functional refractory period was the shortest conducted H_1–H_2 interval. The effective refractory period of the ventricular specialized conducting system was the longest H_1–H_2 interval at which H_2 failed to conduct to the ventricles.

Glucagon was administered intravenously in a dose of 50 μg/kg to each patient after control recordings. Electrophysiologic studies were repeated 5 to 10 minutes after the infusion. In two patients with rate-dependent bundle branch block, the paced rates at which the block appeared before and after administration of the drug were also determined. Statistical analysis of all data was performed using the Student *t* test for paired data.

Results (Table I)

Intraatrial conduction: The P–A interval was measured in all patients (Fig. 1). The mean P–A interval ± standard error of the mean was 35 ± 1.4 msec before and 30 ± 1.5 msec after administration of glucagon (P <0.001). Atrial functional and effective refractory periods could be measured in 21 patients (Fig. 2). The mean functional refractory period

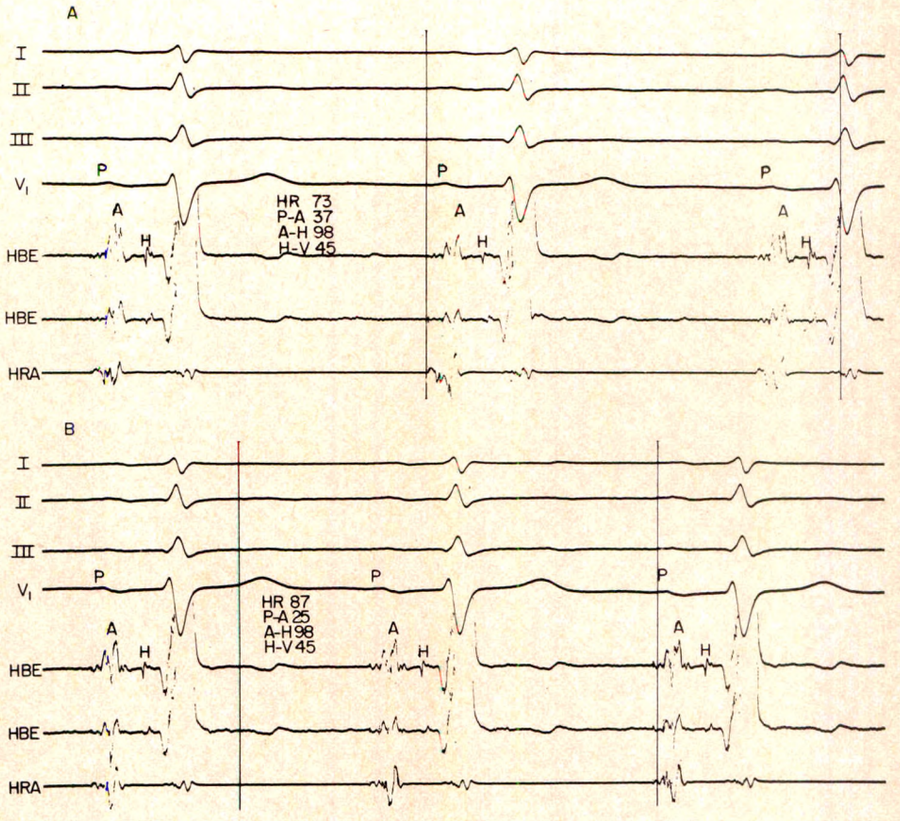

FIGURE 1. Case 3. Conduction intervals before (**A**) and after (**B**) administration of glucagon. Shown are electrocardiographic leads I, II, III and V_1, His bundle electrogram (HBE), and a bipolar intracardiac high right atrial electrogram (HRA). P waves are labeled P, atrial electrogram A and His bundle potentials H. The heart rate (HR) and electrophysiologic intervals are listed. The conduction intervals listed are the means of 10 consecutive beats.

of the atrium was 273 ± 11.6 msec before and 256 ± 10 msec after administration of the drug (P <0.001). The mean effective refractory period of the atrium was 252 ± 12 msec before and 238 ± 9.6 msec after infusion of glucagon (P <0.01). No measurable change in P wave duration was noted after administration of glucagon.

A–V nodal conduction: A–H intervals could be measured in all patients (Fig. 1). The mean A–H interval during sinus rhythm was 97 ± 6 msec before and 96 ± 6 msec after administration of glucagon (not significant). With atrial pacing A–H intervals at equivalent paced rates (90 to 140/min) were not significantly different before and after infusion of glucagon. For example, the mean A–H interval at a paced rate of 100/min in 21 patients was 114 ± 6.4 msec before and 114 ± 6.6 msec after the infusion (not significant). The paced rate at which Wenckebach periods proximal to the His bundle occurred was noted in 21 patients. This mean rate was 144 ± 6 beats/min before and 149 ± 6 beats/min after administration of glucagon (P <0.05). The mean A–V nodal functional refractory period was 465 ± 22 msec before and 457 ± 23 msec after the infusion (not significant). The effective refractory period of the A–V node was 404 ± 33 msec before and 395 ± 32 msec after administration of glucagon (not significant).

Intraventricular conduction: H–V intervals could be measured in 25 patients (Fig. 1). The mean H–V interval was 48.0 ± 2.6 msec before and 49.0 ± 2.0 msec after administration of glucagon (not significant). In one of two patients with rate-dependent left bundle branch block, the critical paced rate for producing left bundle branch block was increased from 110 to 120/min, and in the other patient the critical rates were identical (90/min) both before and after the infusion (not significant). No improvement of conduction was observed in one patient with complete heart block distal to the H potential.

The effective refractory period of the ventricular specialized conduction system could be measured in only two patients, before and after administration of glucagon, because the A–V node limited conduction. The mean values were, respectively, 440 ± 45 msec before and 425 ± 55 msec after the infusion (not significant).

Automaticity and recovery periods of the sinus node: The effect of glucagon on automaticity of the sinus node was evaluated in all patients. Sinus rate increased in all patients. The mean sinus rate was 73 ± 3 beats/min before and 81 ± 3 beats/min after administration of glucagon (P <0.001). Sinus nodal recovery times decreased after glucagon (Fig. 3). Mean recovery times before and after infusion of glucagon were 1,025 ± 42 msec and 919 ± 27 msec, respectively (P <0.01).

Arrhythmias: Premature ventricular contractions were noted in three patients before administration of glucagon. In two, these disappeared completely and in one they became more frequent after administra-

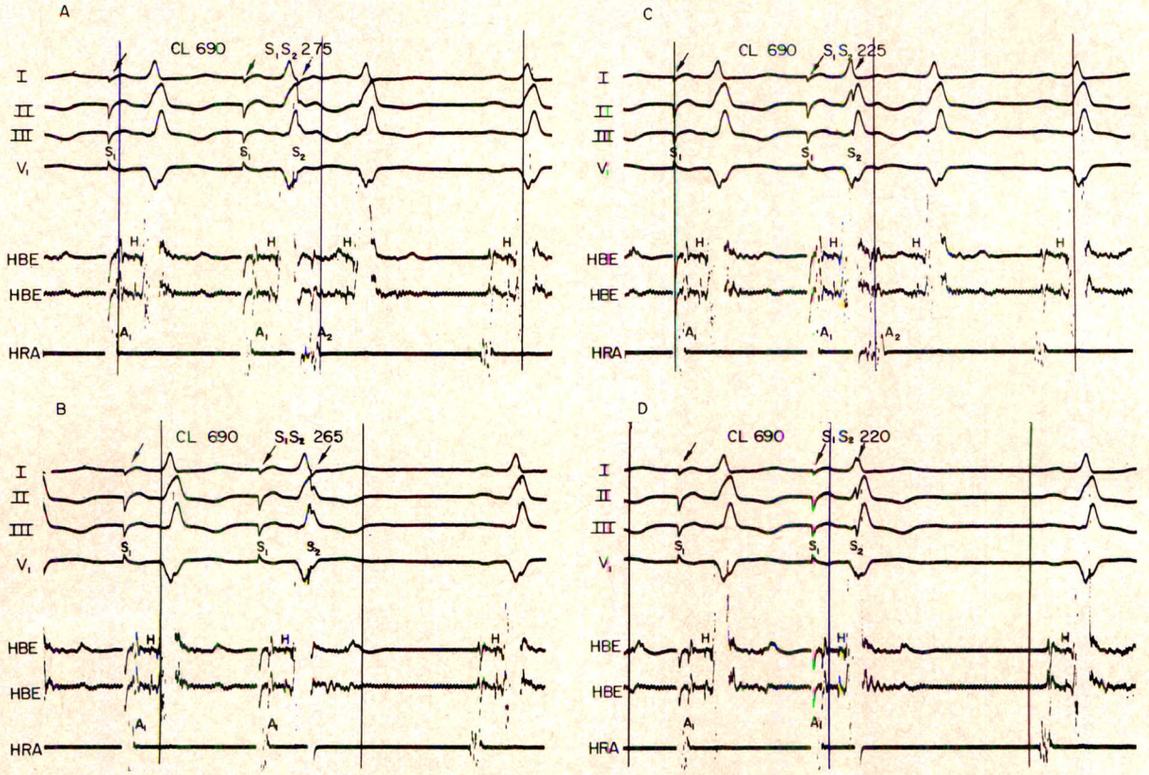

FIGURE 2. Case 11. Measurement of atrial refractory periods before and after administration of glucagon. Paper speed is 100 mm/sec and time lines are at 1 second intervals. The cycle length (CL) of the basic drive (S_1) is 690 msec and the atrial coupling interval (S_1–S_2) is listed at the top of each panel. A_1 is the atrial electrogram induced by S_1, and A_2 is the atrial electrogram of the extrastimulus. **A** and **B** are control recordings, **C** and **D** were obtained after administration of glucagon. **A,** at a coupling interval of 275 msec, S_2 is conducted to the atrium (and ventricle). The A_1–A_2 interval is 295 msec and is the shortest attainable A_1–A_2 interval, defining the functional refractory period of the atrium before administration of glucagon. **B,** S_2 fails to capture the atrium at a coupling interval of 265 msec. This defines the effective refractory period of the atrium before administration of glucagon. **C,** at a coupling interval of 225 msec, S_2 is conducted to the atrium (and ventricle). The A_1–A_2 interval is 260 msec and is the shortest attainable A_1–A_2 interval, defining the functional refractory period of the atrium after administration of glucagon. **D,** S_2 fails to capture the atrium at a coupling interval of 220 msec. This defines the effective refractory period of the atrium after administration of glucagon.

tion of glucagon. In one patient multiple premature atrial contractions, observed in the control period, occurred less frequently after administration of glucagon. No new arrhythmias were observed after administration of the drug.

Discussion

Farah and Tuttle[18] reported that glucagon produced a positive inotropic and chronotropic effect on the heart of several species including canines. Experimental studies in dogs by Whitsitt and Lucchesi[10] revealed that glucagon was capable of rapidly reversing the depression of A–V conduction induced by propranolol. In their study, A–V nodal conduction was evaluated by examining A–V intervals (the time required by an impulse to travel from an atrial stimulating electrode to a ventricular recording electrode) before and after administration of glucagon.

Steiner et al.[11] using the His bundle recording technique, also studied the electrophysiologic effects of glucagon in dogs. They reported facilitation of A–V conduction as manifested by a 26 to 30 percent decrease in the P–H interval after administration of glucagon, but no effect on the H–V interval. They also noted that glucagon reversed the depressant effect of propranolol on A–V conduction. Lipski et al.[12] demonstrated similar facilitation of canine A–V nodal conduction after glucagon, as suggested by a 21 percent decrease in the P–H interval after administration of the drug.

Data on the electrophysiologic effects of glucagon on A–V conduction in man are limited. Nishimura et al.[13] studied the effects of glucagon in 11 patients and found no change in the P–R interval with glucagon. They also noted an insignificant decrease in the P–H interval by 15 msec in the two patients who had His bundle electrogram recordings. The H–V interval was unchanged in these two patients.

Electrophysiologic Effects of Glucagon

The results of our study partially confirm previous observations. The P–A interval, a measure of conduction from the high to the low right atrium, decreased in 22 of 26 patients after administration of glucagon. In addition, glucagon induced a significant decrease in atrial functional and effective refractory periods. These observations suggest that glucagon facilitates intraatrial conduction. The cellular basis for this fa-

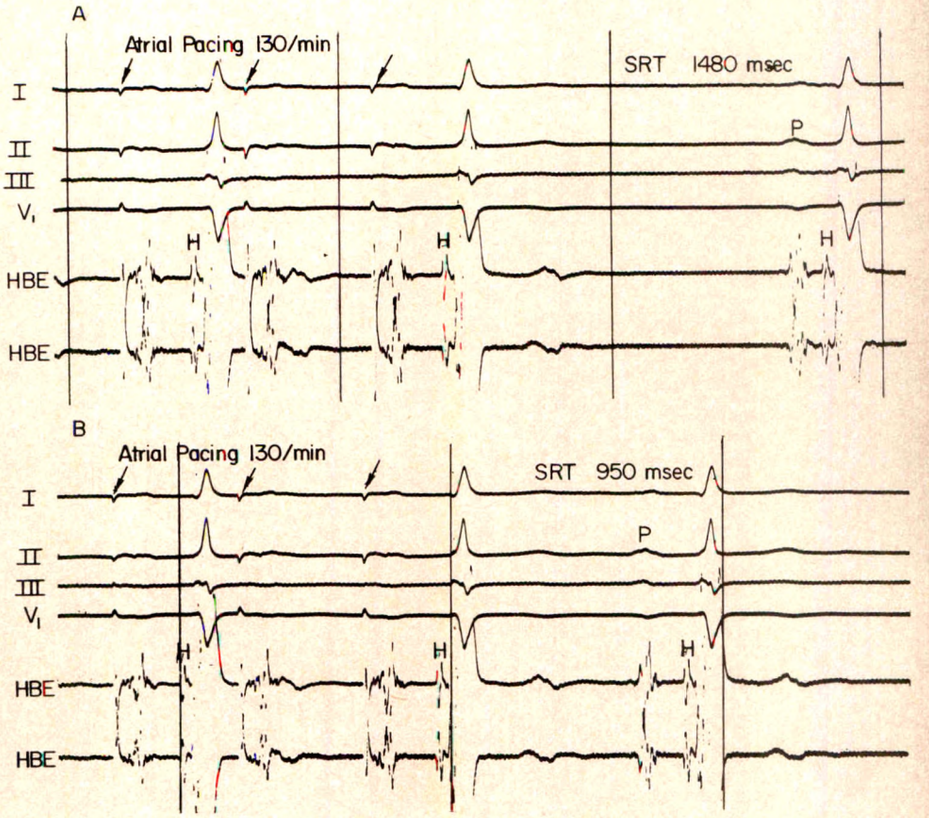

FIGURE 3. Case 2. Recordings demonstrating sinus nodal recovery times (SRT) before (**A**) and after (**B**) administration of glucagon. Atrial pacing spikes are labeled with **arrows,** the pacing rate is 130/min. At this rate 2:1 A–V block proximal to the His potential is present.

cilitation of intraatrial conduction is not apparent and deserves further study. Our findings suggest that glucagon has a minimal effect on A–V nodal conduction in man. The shortening of the P–H interval (which encompasses the P–A and A–H intervals) or the P–R interval with glucagon previously noted[10–13] in animals and man may partially reflect facilitation of intraatrial conduction. The marked decrease of the P–H interval in dogs may also reflect a species-specific facilitation of A–V nodal conduction. Our results regarding lack of effect on intraventricular conduction are consistent with previously reported observations.[9–13]

The effects of glucagon on the sinus node have been well studied in both animals and man. It has been demonstrated that glucagon has a positive chronotropic effect on the sinus as well as the A–V node.[1,3,4,9–13,19–21] The data from our study on enhanced automaticity of the sinus node are in agreement with previous observations. Sinus rates increased in all patients after administration of glucagon. In addition, glucagon decreased sinus nodal recovery time in 25 of 26 patients. The effect of glucagon on A–V junctional automaticity could not be examined in our study.

There are conflicting reports about the effects of glucagon on ventricular automaticity. Steiner et al.[11] and Lucchesi et al.[22] reported that glucagon had no effect on ventricular automaticity in dogs. In contrast, several other workers[12,23,24] have shown an increase in ventricular automaticity in animals induced by glucagon. Wilkerson et al.[24] demonstrated in dogs that glucagon increased ventricular automaticity and that this increase was masked by the positive chronotropic action of the drug on the sinus or A–V node, or both. Nishimura et al.[13] demonstrated in man that glucagon did not significantly change the ventricular automaticity in patients with A–V block. In our patient with complete heart block, the ventricular rate was not increased after administration of glucagon.

It has been suggested that glucagon possesses antiarrhythmic properties since it has been noted to abolish digitalis-induced ventricular arrhythmias.[25–27] In contrast, Lipski et al.[12] observed multiple premature ventricular contractions after administration of glucagon, suggesting that this drug increased ventricular irritability. In two of our three patients with premature ventricular contractions, the ectopic beats were abolished by glucagon whereas they became more frequent in the third patient. In our patients, no new arrhythmias were noted after administration of glucagon, thus suggesting that glucagon is not arrhythmogenic in man. We cannot draw any conclusions about the antiarrhythmic properties of glucagon from this study.

Clinical Implications

Glucagon, in a dose of 50 μg/kg intravenously, produced slight but significant facilitation of intraatrial conduction without demonstrably affecting either

A–V nodal or intraventricular conduction. In addition, this agent produced a modest increase in automaticity of the sinus node, as manifested by an increase in sinus rate and a decrease of sinus nodal recovery time. Glucagon did not appear to be arrhythmogenic.

Although these effects are of pharmacologic interest, they should not play a major role in the decision to use or not to use glucagon as a positive inotropic agent in the management of cardiogenic shock or congestive heart failure. In a clinical situation, glucagon would probably not depress conduction, and thus could be used safely in patients with conduction disease. Its lack of arrhythmogenic properties gives it an advantage over catecholamines in the management of low output states. Our results suggest that glucagon will not be useful in the management of block in the A–V node or His-Purkinje system. The potential value of glucagon in patients with depressed sinus nodal function needs further study.

Acknowledgment

We express our appreciation to Mrs. Alyce Bode and Miss Verneal Banks for secretarial assistance and to Mrs. Loretta Kasparas for technical help.

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Beneficial Electrophysiologic Effects of Nitroglycerin During Acute Myocardial Infarction

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Nitroglycerin reduces ischemic injury after experimental coronary occlusion. To determine whether it also has the potential of protecting the heart against the development of serious ventricular arrhythmias, the effects of nitroglycerin on electrical stability of acutely ischemic myocardium were determined in open chest dogs. Electrical stability of the ventricle was assessed by measuring ventricular fibrillation threshold before and after acute myocardial ischemia was produced by occlusion of the left anterior descending coronary artery. Ventricular fibrillation threshold was measured in a random manner under conditions of nonischemia, ischemia, ischemia plus nitroglycerin, and simultaneous infusion of phenylephrine to maintain mean systemic arterial pressure at control levels. Heart rate was kept constant at 120 beats/min by destruction of the atrioventricular node and use of ventricular pacing. In the absence of ischemia ventricular fibrillation threshold was 77 ± 5 milliamperes (ma), a value unaffected by either nitroglycerin or phenylephrine. After 6 minutes of acute myocardial ischemia, ventricular fibrillation threshold was reduced to 30 ± 6 ma ($P < 0.01$). When nitroglycerin was infused at a rate of 200 μg/min (with a reduction in arterial pressure of 24 percent), ventricular fibrillation threshold after 6 minutes of acute ischemia increased from 30 ± 6 to 55 ± 3 ma ($P < 0.005$). Restoration of arterial pressure by phenylephrine during infusion of nitroglycerin further raised the ventricular fibrillation threshold to 75 ± 6 ma, a value identical to that present in nonischemia. Thus, nitroglycerin enhances electrical stability of the heart during experimental acute myocardial ischemia, an effect probably related to reduction of ischemic injury. Since the ventricular fibrillation threshold increases even further after arterial pressure is restored to control levels, this beneficial electrophysiologic effect is probably caused by some action of nitroglycerin other than reduction in myocardial oxygen consumption mediated by decreased afterload.

Despite the long-standing use of nitroglycerin in the treatment of angina pectoris, it is generally accepted that the drug should not be used to treat ischemic pain caused by acute myocardial infarction. This concept is based on the belief that the nitroglycerin-induced decrease in arterial pressure and reflex increase in heart rate might exacerbate the ischemic insult. The demonstration that hypotension (induced either by hemorrhage[1] or reflexly by stimulation of the carotid baroreceptors[2]) and an increase in heart rate[3] augment the degree of ischemic injury occurring during experimental acute coronary occlusion appears to support this view.

Recently, the concept that nitroglycerin is contraindicated in acute myocardial infarction has been challenged by the finding that during experimental coronary occlusion, nitroglycerin actually diminishes the intensity of ischemia[1] and the area of infarcted myocardium.[4] If these beneficial effects are of physiologic significance, and if the pro-

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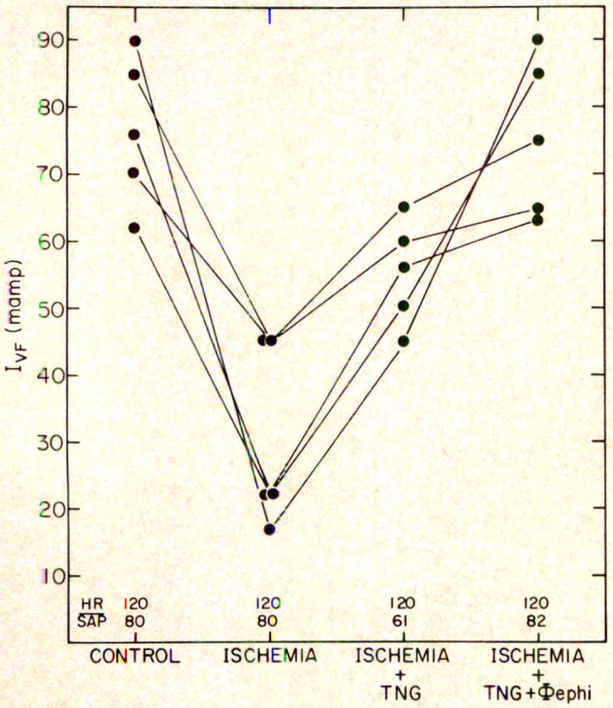

FIGURE 1. Ventricular fibrillation threshold (I_{VF}) in 5 dogs under conditions of nonischemia, ischemia, ischemia with nitroglycerin (TNG) infusion, and ischemia with nitroglycerin and phenylephrine (Φephi). Heart rate (HR) was kept constant by ventricular pacing. $\overline{SAP}$ = mean systemic arterial pressure.

pensity for arrhythmias to develop during coronary occlusion is related to the degree of associated myocardial ischemia, nitroglycerin might also counteract the diminution of electrical stability in ischemic myocardium.[5] In this study we tested this hypothesis by determining the effect of nitroglycerin on the vulnerability of the ventricle to fibrillation during experimental acute myocardial ischemia.

Methods

Mongrel dogs weighing from 15 to 18 kg were anesthetized with sodium pentobarbital, 30 mg/kg intravenously, and studied in the supine position. The heart was exposed through a transverse thoracotomy and an adjustable ligature was placed around the left anterior descending coronary artery approximately 2 cm from its origin. Heart rate and systemic arterial pressure were recorded continuously. Heart rate was kept constant at 120 beats/min with ventricular pacing after induction of complete heart block by the injection of 1 ml of 10 percent formalin into the region of the atrioventricular (A–V) node.

Ventricular fibrillation threshold was assessed by delivering a train of pulses, each 2 msec in duration and separated by 8 msec, through a bipolar platinum electrode sutured to the left ventricle outside of the region of subsequent ischemia. The train of pulses was delivered during the ventricular vulnerable period, starting 80 msec after ventricular activation and continuing for 50 msec after the end of the T wave in lead II of the electrocardiogram. The current was increased by four milliampere (ma) steps (measured with a Hewlett-Packard current probe and displayed on a storage oscilloscope) until ventricular fibrillation occurred. Ventricular fibrillation threshold was defined as the current (in milliamperes) required to produce fibrillation. This procedure was similar to that previously described.[5] Ventricular defibrillation was accomplished within 30 seconds after the initiation of fibrillation by a direct current shock (capacitor-discharged) applied to the heart through two 6 cm electrodes.

Ventricular fibrillation threshold was determined under four conditions: (1) in the absence of ischemia, (2) during ischemia (5 minutes after occlusion of the left anterior descending coronary artery), (3) during ischemia when nitroglycerin was being administered, and (4) during ischemia with simultaneous administration of nitroglycerin and phenylephrine. When nitroglycerin was administered it was given before coronary occlusion as a single injection of 300 μg followed by a constant infusion of 200 μg/min. When phenylephrine was administered it was given after the effects of the nitroglycerin infusion had stabilized and was infused at a rate sufficient to maintain systemic arterial pressure at control levels. The interventions were randomized, and each was separated by a 1 hour period. (We recently demonstrated[5] that ventricular fibrillation threshold during acute myocardial ischemia under control conditions of arterial pressure and heart rate was unchanged over a time course similar to that used here.) The effects on ventricular fibrillation threshold in the absence of ischemia of nitroglycerin alone, phenylephrine alone and the combination of nitroglycerin and phenylephrine were determined in two dogs.

Statistical analysis was performed by Student's *t* test for paired data. Results are expressed as mean ± 1 standard error of the mean.

Results

Systemic Arterial Pressure

Occlusion of the left anterior descending coronary artery at a heart rate of 120 beats/min did not induce any changes in systemic arterial pressure. Administration of nitroglycerin (300 μg intravenously followed by an infusion of 200 μg/min) caused mean systemic arterial pressure to decrease from 80 ± 6 to 61 ± 3 mm Hg ($P < 0.05$). Infusion of phenylephrine during administration of nitroglycerin restored arterial pressure to control values.

Ventricular Fibrillation Threshold

Nonischemia: Ventricular fibrillation threshold averaged 77 ± 5 ma in the five experimental animals. In two additional control animals nitroglycerin and phenylephrine were administered separately and in combination in the doses previously described. In the first of these two animals under control conditions the fibrillation threshold was 62 ma, during infusion of nitroglycerin alone 60 ma (systemic arterial pressure decreased 20 percent), during infusion of phenylephrine alone 68 ma (arterial pressure increased 10 percent) and with the combined administration of nitroglycerin and phenylephrine 66 ma (arterial pressure unchanged). In the second animal the fibrillation threshold under control conditions was 76 ma, during infusion of nitroglycerin alone 70 ma (arterial pressure decreased 22 percent), during infusion of phenylephrine alone 80 ma (arterial pressure increased 16 percent) and with the combined adminis-

tration of nitroglycerin and phenylephrine 74 ma (arterial pressure unchanged).

Effects of ischemia: Ventricular fibrillation threshold decreased 61 percent from control (nonischemic) values 5 minutes after occlusion of the left anterior descending coronary artery. The fibrillation threshold was lowered from an average of 77 ± 5 to 30 ± 6 ma ($P < 0.01$, Fig. 1).

Effects of nitroglycerin during acute myocardial ischemia: When nitroglycerin was infused during coronary occlusion ventricular fibrillation threshold increased 83 percent from the level reached during ischemia in the absence of nitroglycerin (Fig. 1). The improvement occurred despite a 24 percent reduction in mean arterial pressure. Thus, fibrillation threshold averaged 30 ± 6 ma during myocardial ischemia under control conditions and 55 ± 3 ma during ischemia when nitroglycerin was infused ($P < 0.005$).

Effects of nitroglycerin and phenylephrine during acute myocardial ischemia: When the nitroglycerin-induced reduction in arterial pressure was prevented by the simultaneous administration of phenylephrine, ventricular fibrillation threshold during acute myocardial ischemia increased even further to 75 ± 6 ma (Fig. 1). This value was not significantly different from the control (nonischemia) fibrillation threshold (mean difference 2 ± 8 ma).

Discussion

The results of our investigation demonstrate that nitroglycerin increases the electrical stability of acutely ischemic myocardium, as manifested by a decreased vulnerability of the heart to the development of ventricular fibrillation in response to an electrical stimulus. Moreover, this beneficial electrophysiologic effect is potentiated when the nitrate-induced hypotension is prevented by the simultaneous administration of phenylephrine, an alpha receptor agonist. The potential efficacy of combination therapy appears considerable, since the decrease in electrical stability that occurred during ischemia was completely reversed by simultaneous administration of nitroglycerin and phenylephrine.

The absolute values for the ventricular fibrillation threshold in these experiments were considerably higher than those previously reported from our laboratory[5] and by others[6,7] in anesthetized open chest dogs. The only difference between this preparation and those of previous studies, in which fibrillation thresholds were lower, was that in the studies described here the A–V node was destroyed by formalin in order to induce heart block. The latter was required to achieve slower heart rates than those usually obtained in pentobarbital-anesthetized dogs. The mechanism responsible for the increased threshold for fibrillation caused by the induction of heart block is unknown. However, there are several possible explanations. The formalin injection in the A–V nodal region could have interrupted sympathetic nerve fibers to the ventricular conducting system. Stimulation of these fibers is known to decrease the ventricular fibrillation threshold.[8] Destruction of the A–V nodal region also could have destroyed some of the particularly vulnerable areas of the conducting system. The elucidation of the exact mechanism responsible for the increased ventricular fibrillation threshold in animals with heart block requires further study.

Mechanism of effect of nitroglycerin on ventricular fibrillation threshold: How nitroglycerin reverses the ischemia-induced decrease in electrical stability cannot be determined precisely from the results of our investigation. Nitroglycerin increased fibrillation threshold only in the presence of ischemia. Thus, it is unlikely that its actions were due to a nonspecific membrane-stabilizing effect although such direct effects could be demonstrable only in ischemic tissue. Alternatively, the beneficial electrophysiologic effect could have resulted from a favorable change in the balance between myocardial oxygen supply and demand within the ischemic zone. This mechanism would be operative if nitroglycerin reduced oxygen demands of the ischemic tissue by altering heart rate, wall tension and myocardial contractile state. However, the beneficial effects of nitroglycerin were observed even when heart rate and arterial pressure were kept constant, and under these conditions reduction of myocardial contractility also would have been unlikely. Thus, if nitroglycerin caused a significant decrease in myocardial oxygen consumption under the conditions of our study, it could have done so only by causing greater venodilatation than could be reversed by phenylephrine. This change would decrease ventricular volume, diminish myocardial wall tension and thereby decrease myocardial oxygen consumption.

Finally, nitroglycerin could have favorably altered the balance between myocardial oxygen supply and demand by increasing blood flow to the ischemic area. Nitroglycerin has been shown in the dog to be capable of dilating large coronary arteries, increasing retrograde coronary flow during coronary occlusion, and increasing coronary pressure distal to the site of an occluded coronary artery.[9] Winbury et al.[10] have shown an increase in endocardial PO_2 and a favorable redistribution of blood toward ischemic myocardium after administration of nitroglycerin. Recent studies from our laboratory[11] have demonstrated that nitroglycerin has the capacity to decrease resistance to collateral flow in patients undergoing coronary bypass surgery.

The increase in ventricular fibrillation threshold after administration of nitroglycerin is not necessarily equivalent to a decreased propensity for the *spontaneous* development of serious ventricular arrhythmias and ventricular fibrillation. However, data presented elsewhere in this issue [12] suggest that this is the case.

Clinical implications: Recently, additional data have been reported that suggest a role for nitroglycerin in the therapy of acute myocardial infarction. For example, the degree of ischemic injury occurring during experimental acute coronary occlusion is di-

minished by nitroglycerin, and this effect is further enhanced when the reduction in arterial pressure is prevented by the infusion of an alpha adrenergic agonist.[1] Later studies have shown that the extent of myocardial infarction (quantitated by measuring the depression of myocardial creatine phosphokinase activity) produced by 5 hours of occlusion of the left anterior descending coronary artery is considerably less in dogs treated by an infusion of nitroglycerin and methoxamine than in a control group.[4] In addition, Gold et al.[13] administered nitroglycerin sublingually to a group of patients with acute myocardial infarction. In some of the patients with persistent refractory left ventricular failure, nitroglycerin resulted in a reduction in pulmonary capillary wedge pressure and an increase in cardiac output. Similar results were obtained by Franciosa et al,[14] who infused the vasodilator, sodium nitroprusside, in patients with acute infarction. The results of our investigation, which demonstrate that nitroglycerin also enhances electrical stability, add another dimension to the potential beneficial role of nitroglycerin in acute myocardial infarction. Thus, although it is not certain whether our data are applicable to the clinical situation, they suggest that nitroglycerin may be uniquely valuable in the treatment of acute myocardial infarction by reducing the degree of ischemic injury and the incidence of serious ventricular arrhythmias.

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Nitroglycerin-Induced Reduction in the Incidence of Spontaneous Ventricular Fibrillation During Coronary Occlusion in Dogs

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Previous investigations have demonstrated that nitroglycerin reduces ischemic injury and enhances ventricular electrical stability during coronary occlusion in dogs. These beneficial effects were potentiated by preventing drug-induced hypotension with alpha adrenergic agonists. To determine whether nitroglycerin can prevent spontaneous post-occlusion ventricular fibrillation, 27 open chest dogs were assigned in random fashion to two groups—control (saline infusion) and nitroglycerin-treated (0.45 mg intravenous bolus infusion followed by 0.3 mg/min continuous infusion). After 10 minutes of infusion the left anterior descending and septal coronary arteries were occluded at their origins. Hypotensive effects of nitroglycerin were prevented by intermittent intravenous doses of methoxamine; mean arterial pressure and heart rate in control and treated animals were thus indistinguishable. Infusions continued until ventricular fibrillation occurred or 30 minutes elapsed. Twelve of 13 control dogs died with ventricular fibrillation; only 7 of 14 nitroglycerin-treated dogs died ($P < 0.05$). Thus, nitroglycerin may be capable of exerting important and unique beneficial effects in patients with acute myocardial infarction since, with its hypotensive effects obviated by alpha adrenergic agonists, it markedly diminishes ischemic injury, enhances ventricular electrical stability, and significantly reduces the incidence of spontaneous ventricular fibrillation in an experimental model of acute myocardial infarction.

The use of nitroglycerin traditionally has been avoided in the presence of acute myocardial infarction because of the fear that nitroglycerin-induced hypotension and tachycardia might exacerbate the ischemic insult. Recently, however, nitroglycerin was found to reduce the degree of ischemic injury and to increase the threshold at which ventricular fibrillation could be induced electrically during experimental acute coronary occlusion[1–4]; both of these salutary effects were enhanced if nitroglycerin-induced hypotension was prevented by administration of an alpha adrenergic agonist. In this investigation we have determined whether nitroglycerin is capable of inhibiting the *spontaneous* occurrence of ventricular fibrillation during acute coronary occlusion in dogs when drug-induced hypotension is prevented with methoxamine.

Methods

Twenty-seven male dogs weighing 16 to 25 kg were randomized into control and nitroglycerin-treated groups. Each dog was anesthetized with intravenously administered sodium pentobarbital (35 mg/kg). A catheter was introduced into the femoral artery for pressure recording and into a limb vein

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for drug administration. Standard subcutaneous electrodes were inserted for recording the electrocardiogram. The heart was exposed through a left thoracotomy during positive pressure ventilation. The left anterior descending and septal coronary arteries were dissected free at their origins. Arterial hemoglobin oxygen saturation and pH were then determined and the respirator adjusted so that oxygen saturation was at least 91 percent, and pH was between 7.42 and 7.52. All dogs had sinus rhythm. Each dog in the treated group received an initial intravenous bolus infusion of 0.45 mg of nitroglycerin followed by a continuous intravenous infusion of 0.3 mg/min. The infusion solution was prepared by dissolving nitroglycerin tablets (Lilly) in normal saline solution in quantities permitting an infusion rate of 0.5 ml/min. Methoxamine, an alpha adrenergic agonist, was administered intermittently to maintain mean arterial pressure at the pre-nitroglycerin level. Each control dog received an infusion of normal saline solution, also at a rate of 0.5 ml/min. After 10 minutes of infusion, the left anterior descending and septal coronary arteries were simultaneously clamped at their origins; the clamp was suspended by sutures from an overlying crossbar so that traction on the coronary arteries was relatively constant despite respiratory movements. The clamp was carefully placed so as to avoid occluding either the left main or left circumflex coronary arteries. To ensure that such inadvertent occlusion had not occurred, after each experiment the heart was removed with the clamp in place and the coronary arteries were probed, opened and inspected. Mean arterial pressure and the electrocardiogram were recorded continuously.

After occlusion, each experiment continued until the dog died with ventricular fibrillation, or until 30 minutes had elapsed without ventricular fibrillation. This duration of observation was chosen since preliminary experiments with this model demonstrated that if fibrillation did not develop within 30 minutes after occlusion, it did not develop during a subsequent hour of observation either in control or nitroglycerin-treated dogs.

The rate of administration of methoxamine as well as nitroglycerin was identical in treated dogs that experienced ventricular fibrillation and in treated survivors.

Statistical analysis of the difference in incidence of ventricular fibrillation in control and treated groups was performed with the use of the Fisher Exact Test. Comparison of blood pressure and heart rate was performed with the Student *t* test.

Results

Before infusion, no significant differences in mean arterial pressure or heart rate existed between control and treated dogs. Mean arterial pressure in control dogs was 120 ± 5 mm Hg and in treated dogs 128 ± 6 mm Hg. Heart rate in control dogs was 166 ± 7 beats/min and in treated dogs was 170 ± 6 beats/min. Moreover, during the course of occlusion, no significant differences developed between the control and treated dogs that were alive at any given assessment point. Arterial pressure remained relatively constant in each dog for the duration of the experiment, except for transient fluctuations associated with arrhythmias which, when ventricular fibrillation did not supervene, were only of a few seconds' duration. Among the treated dogs, no significant differences in heart rate or blood pressure were discernible during the course of the experiments when comparing the dogs that died with those that survived.

Ventricular fibrillation occurred in 12 of 13 control dogs but in only 7 of 14 treated dogs ($P < 0.05$, Fig. 1). No dog had ventricular fibrillation after surviving more than 18.5 minutes of occlusion, and most (15 of 19) died between 11 and 18.5 minutes after occlusion. No dog had atrioventricular dissociation during the course of the experiment.

Discussion

The results of this investigation demonstrate that nitroglycerin (its hypotensive effects obviated by simultaneous administration of methoxamine) markedly diminishes the incidence of ventricular fibrillation occurring spontaneously in an experimental model of acute myocardial infarction. These results are in accord with and extend our previous studies[3,4] demonstrating that nitroglycerin, alone or with phenylephrine, significantly increases the threshold at which ventricular fibrillation can be induced electrically during coronary occlusion in dogs.

Mechanisms of beneficial action of nitroglycerin: The mechanisms by which nitroglycerin and methoxamine reduce the prevalence of ventricular fibrillation are unknown. Nitroglycerin alone, and in combination with methoxamine, decreases the degree of myocardial ischemia occurring during experimental coronary occlusion.[1,2] It appears likely that such an effect is responsible for enhanced survival. This conclusion is reinforced by our previous findings that nitroglycerin increases ventricular fibrillation threshold in the presence of ischemia but does not do so when ischemia is absent. It is unclear, however, whether nitroglycerin reduces ischemia by decreasing oxygen demand of the heart, increasing blood flow to ischemic areas, or both.

The actions of nitroglycerin alone on the prevalence of spontaneous ventricular fibrillation during

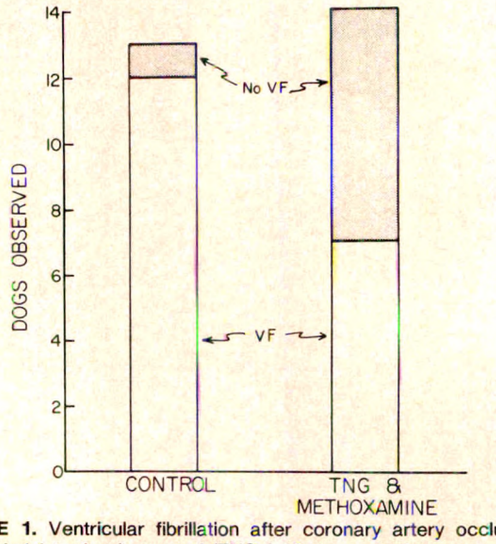

FIGURE 1. Ventricular fibrillation after coronary artery occlusion. Drug administration in treated (TNG & Methoxamine) group and saline infusion in control group were begun 10 minutes before coronary occlusion.

coronary occlusion is yet to be determined. That this agent contributes markedly to the decrease in ventricular fibrillation observed when both nitroglycerin and methoxamine are administered, however, is suggested by the finding that nitroglycerin itself increased ventricular fibrillation threshold during acute myocardial ischemia.[3,4] When the hypotensive effects of nitroglycerin were abolished by simultaneous administration of another alpha adrenergic agonist (phenylephrine), a further increase in ventricular fibrillation threshold was observed. Moreover, we have found no significant reduction in the incidence of spontaneous postocclusion fibrillation after the administration of phenylephrine alone, in amounts sufficient to raise mean arterial pressure to levels associated with significant reduction in ischemic injury (unpublished observations). Thus, the results of the previous studies, in conjunction with those of this investigation, indicate that nitroglycerin can inhibit the development of ventricular fibrillation occurring during experimental acute coronary occlusion and that this effect is potentiated by preventing the reduction in arterial pressure that this drug might cause.

The dog model of ischemia-induced ventricular fibrillation used in the present investigation differs considerably from models used in other studies. In such models, although wide fluctuations exist, the incidence of early ventricular fibrillation has generally been far lower than in the present model, whereas hemodynamic abnormalities have often been prominent. Thus, although occlusion of the left main coronary artery leads almost uniformly to ventricular fibrillation, this intervention usually causes hypotension and cardiogenic shock.[5–7] When the circumflex coronary artery is occluded in the open chest dog, the cumulative incidence of ventricular fibrillation is about 33 percent.[5,8,9] In the closed chest dog, the incidence has been approximately 60 percent, but the range from study to study is extensive (0 to 75 percent) and severe hypotension is a frequent complicating feature.[7,8,10–12] Approximately 30 percent of more than 750 closed and open chest dogs studied have had fibrillation within 30 minutes after proximal occlusion of the left anterior descending coronary artery[5,8,9,13–18]; in combined small series about 10 percent of dogs had early fibrillation after occlusion of the septal artery.[5,19,20] The incidence of ventricular fibrillation after occlusion of the right coronary artery is 10 percent.[5,7,9,21] In this study, the septal coronary artery was systematically occluded together with the left anterior descending coronary artery. Both vessels were occluded proximal to any branches. This intervention led to incidence of ventricular fibrillation of 92 percent in the control group. In more recent studies from our laboratory in which the same model has been used, the cumulative incidence of fibrillation in untreated animals has been 87 percent (71 of 82). Changes in blood pressure and heart rate after occlusion have been relatively slight in virtually all studies, and are comparable to those reported here. Moreover, our data indicate that the model can be influenced by therapeutic interventions, despite the ischemic insult and high rate of ventricular fibrillation. Hence, this model of acute infarction appears to have particular advantages for evaluating interventions that are capable of reducing the incidence of spontaneous ventricular fibrillation during the early phase of acute myocardial infarction.

Clinical implications: The applicability of our findings to acute myocardial infarction in man is unknown. The protective effects of nitroglycerin on the occurrence of ventricular fibrillation were demonstrated in dogs with acute coronary occlusion but with otherwise normal coronary arteries and normal myocardium. It is possible that nitroglycerin does not exert similar effects when long-term multivessel disease is present. Moreover, other workers[22] have demonstrated that the mechanism of ventricular fibrillation is different early after coronary occlusion than it is several hours later. Thus, although our results suggest potential benefit from nitroglycerin (with methoxamine) during the early phase of acute myocardial infarction in man (when most arrhythmic deaths occur[23,24]), the drug may not have similar effects later in the course of infarction.

There is now an impressive body of experimental evidence demonstrating that during acute coronary occlusion nitroglycerin decreases ischemic injury, enhances electrical stability of the ventricle and, as our study has shown, reduces the incidence of spontaneously occurring ventricular fibrillation. Clinical studies[25] indicate that during the course of acute myocardial infarction associated with left ventricular failure in man, administration of nitroglycerin can result in hemodynamic improvement. Thus, these experimental and clinical studies suggest that the general reluctance to administer nitroglycerin during acute myocardial infarction should be reconsidered since the drug may be of unique therapeutic value in this condition.

Acknowledgment

We gratefully acknowledge the expert technical assistance of Mr. Richard McGill and Mr. William Parker.

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Modification of Experimental Myocardial Infarct Size by Cardiac Drugs

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After occlusion of a coronary artery in dogs, regionally ischemic myocardium was delineated by means of a strain gauge-tipped, two pronged catheter probe that measures myocardial fiber shortening. The curves of contraction were sensitive to the effects of ischemia. A central zone of complete ischemia was identified as the region in which fiber shortening was lost and replaced by passive fiber lengthening. As the probe was inched away from the center toward the periphery, an intermediate zone of incomplete ischemia was defined as the region in which contractility was partially diminished but not lost. It was assumed that a shift in oxygen balance induced by an intervention will be reflected as a change in contractility of the intermediate zone. Accordingly, the intermediate zone was used as the test zone to evaluate effects of drugs on the extent of regionally ischemic myocardium. Isoproterenol initially augmented contractility of the intermediate zone but, with continued infusion, a secondary reduction in contractility became evident at 30 to 45 minutes. Norepinephrine augmented contractility of the intermediate zone and this effect persisted through the 1 hour observation period. Ouabain similarly increased the velocity of shortening of the intermediate zone. An increase in left ventricular afterload induced by methoxamine resulted in loss of contractility and its replacement by fiber lengthening in the intermediate zone. These findings indicate that isoproterenol and methoxamine can increase the extent of noncontracting ischemic myocardium and, hence, infarct size. Norepinephrine and ouabain do not exert this effect.

Drugs that augment myocardial contractility or increase arterial pressure, or both, continue to be used to treat pump failure of the heart complicating acute myocardial infarction.[1–5] But the increases in both myocardial contractile state[6] and myocardial wall tension[7] induce an increase in myocardial oxygen consumption. If coronary circulation is impaired, it is postulated that such an increase in oxygen demand may so exceed the rate of oxygen delivery as to accentuate the severity of ischemia and result in an extension of the infarct.[8,9] Maroko et al.[9] recently reported that the severity and extent of ischemic injury after experimental coronary occlusion are increased by cardiac stimulating drugs that increase myocardial oxygen consumption. These observations, based on a study of the magnitude and distribution of S–T segment elevation in the epicardial electrogram, contrast with earlier data from Sayen et al.[10] demonstrating that levarterenol has a favorable effect on the ischemic area.

Earlier preliminary studies from this laboratory[8,11,12] indicated that changes in contractility of the zone of partial ischemia provide a method of evaluating the effect of drugs on the size of a myocardial infarct. The size of the infarct is delineated by means of a previously described strain gauge-tipped catheter probe that measures myocar-

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This work was supported by a grant from the Michigan Heart Association, the estate of Stanley E. Kaminski through Wayne State University School of Medicine and Detroit General Hospital Research Corporation, Detroit Mich. Manuscript accepted August 9, 1973.

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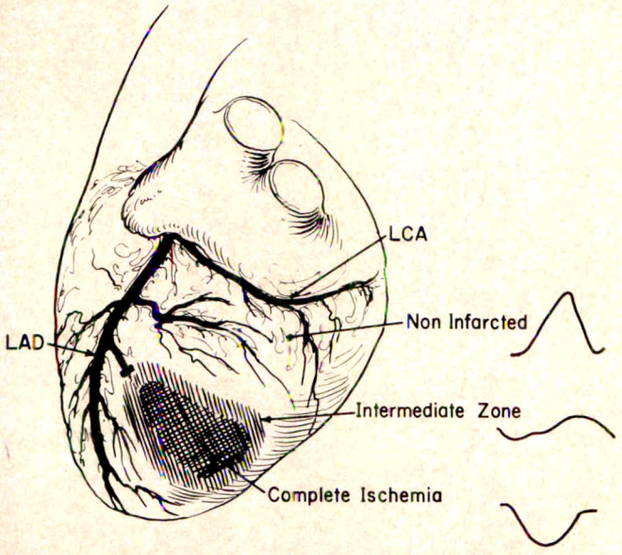

FIGURE 1. Definition of the intermediate zone of partial ischemia after coronary occlusion. In the noninfarcted myocardium, the curve of fiber shortening is inscribed in an upward direction during systole. In the central zone of complete ischemia where contractility is lost, the curve of fiber shortening is replaced by the inverted curve of passive fiber lengthening. As the probe is inched away from the center toward the periphery, an intermediate zone is delineated as the region in which velocity of shortening is diminished by at least 50 percent of the control value. LAD = left anterior descending coronary artery; LCA = left circumflex artery.

dial fiber shortening.[4,13] The probe is used to map segmental changes in myocardial contraction over the surface of the left ventricle.[4,14] Curves of cardiac contraction obtained with the strain gauge probe are extremely sensitive to the effects of ischemia.[4,11] Coronary occlusion results in a rapid loss of myocardial fiber shortening and its replacement by passive fiber lengthening in the center of the ischemic myocardium.[4,8,12] By inching the probe away from the center toward the periphery, one can define an intermediate zone of partial ischemia, interposed between infarcted and noninfarcted myocardial zones, in which contractility is diminished but not lost.[8,11,12] The intermediate zone is used as the test zone to evaluate the effects of drugs on the severity and extent of ischemia because it is assumed that a drug-induced shift in oxygen balance in this zone will be reflected as a primary change in contractility of this region.[8,11,12] Four cardiac drugs with contractile and hemodynamic effects that result in an increase in myocardial oxygen consumption were studied.

Methods

Experiments were performed in 47 mongrel dogs weighing 15 to 22 kg and anesthetized with sodium pentobarbital (25 mg/kg body weight) given intravenously. The trachea was intubated and artificial ventilation, using room air, was instituted by means of a Harvard respirator pump. Thoracotomy was performed in the left fifth intercostal space and the pericardium was opened anterior to the left phrenic nerve. The left anterior descending coronary artery or one of its major branches was mobilized by dissection and a rubber-sheathed curved arterial clamp described previously[4] was used to produce intermittent occlusion. Left ventricular pressure was monitored through a stiff-walled catheter directly connected to a Statham P23Db transducer system and an Electronics for Medicine recorder. Zero level for pressure measurements was set at the mid-chest position. The first derivative of left ventricular pressure pulse (dP/dt) was obtained by means of a resistance-capacitance differentiating circuit. Left ventricular end-diastolic pressure was recorded using higher sensitivity at the end expiratory phase of the respiratory cycle.

Regional contractility: A strain gauge catheter probe that measures myocardial fiber shortening, previously described in detail,[4,13] was used to measure segmental changes in contractility. Briefly, the device consists of two strain gauge-bearing prongs mounted on a stylette. There is a linear relation between the spacing of the prongs and strain in the gauges. The distance between the prongs is 2.5 mm, thus permitting study of curves of contraction over small segments of myocardium. The prongs were extended to the outside of the catheter and were directly inserted into the subepicardial surface of the left ventricular wall. Only the terminal points of the prongs were engaged into the myocardium.[4,13,14] As the prongs follow the course of fiber shortening during systole, curves of contraction are inscribed in an upward direction on a beat to beat basis. The velocity of shortening was measured by drawing a tangent at isolength points relating the height of the curve to time.[13] All recordings were made during expiration.

Regional ischemia: Medium-sized areas of ischemia were produced by occluding one of the major branches of the left anterior descending coronary artery. With use of the strain gauge probe, control curves of contraction were obtained from the region supplied by the artery to be occluded. The probe was positioned in the center of this area and recordings were made continuously as the artery was occluded. In this manner, the exact time course of changes in the curves of contraction was studied. In 15 animals, after a period of occlusion ranging from 5 to 45 minutes, the occlusion was released and recovery of contractility in the ischemic zone studied.

The region immediately surrounding the occluded artery (Fig. 1), in which contractility was lost and replaced by the inverted curve (inscribed downward) of passive fiber lengthening was referred to as the central zone of complete ischemia. As the probe was inched away from the center toward the periphery, an intermediate zone was delineated in which contractility (velocity of shortening) was diminished by at least 50 percent of the control values but not completely lost. This represented the zone of partial ischemia or intermediate zone interposed between infarcted and noninfarcted regions.

Changes in contractility of this zone induced by various drugs were used to assess the effect of these agents on the severity and extent of regionally ischemic myocardium and, hence, infarct size. It is assumed that a drug-induced shift in myocardial oxygen balance will affect the severity of ischemia and, hence, contractility of the intermediate zone. For example, a cardiac stimulating drug is expected to augment contractility through its positive inotropic action. However, should the increase in myocardial oxygen consumption resulting from the increased contractility exceed the oxygen supply, then the resulting negative oxygen balance produced by the increased severity of ischemia may result in a decline of contractility in the intermediate zone. Interventions with an oxygen-sparing action will have an opposite effect.

Protocol: The procedure followed in all experiments was identical. The intermediate zone was delineated 15 minutes

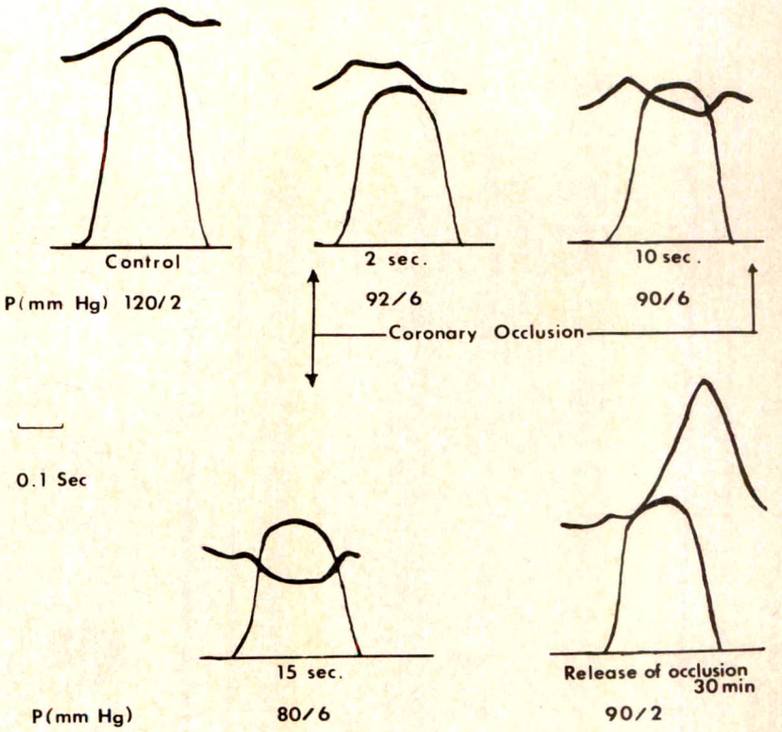

FIGURE 2. Effect of coronary occlusion and release of occlusion on the curves of contraction in 15 dogs. In the control state the curve of myocardial contraction is inscribed in an upward direction. Two seconds after occlusion, the late systolic portion of the curve begins to show inversion. At 10 seconds most of the curve except for the initial component is inverted. At 15 seconds the entire curve is inverted, indicating loss of fiber shortening and its replacement by passive fiber lengthening. After release of coronary occlusion at 30 minutes, the original upward inscription of the curve associated with an initial overshoot is restored, indicating recovery of contractility. P = left ventricular pressure.

after coronary occlusion when hemodynamic variables were stable. Drugs were administered at a constant rate by means of a power-driven infusion pump. Curves of contraction in the intermediate zone were continuously monitored. Recordings were made at 5 minute intervals for 30 to 60 minutes. Measurements were made on the average of 8 to 10 beats for each period of observation with reproducible results; those obtained at the time of optimal response were utilized for statistical analysis using Student's paired *t* test. Each of the four drugs studied was tested in eight dogs; no dog received more than one drug. The following drugs were administered intravenously: isoproterenol (0.25 to 0.50 μg/kg per min), norepinephrine (4.0 μg/min), ouabain (0.5 mg) and methoxamine (1.0 mg/min).

Results

In the control state the systolic curve of myocardial contraction (fiber shortening) is inscribed upward. During diastole, corresponding to myocardial relaxation and fiber lengthening, the curve is inscribed downward (Fig. 1 to 6).

Coronary occlusion resulted in an immediate decline in the amplitude of the curve of contraction in the central zone (Fig. 2). At 2 to 5 seconds, the late systolic portion of the curve was inverted and at 15 to 30 seconds the entire curve was inscribed downward, indicating loss of systolic fiber shortening and its replacement by dyskinetic passive fiber lengthening. If coronary occlusion was released and flow restored at any time up to 45 minutes, the original upward inscription of the curve returned, indicating recovery of contractility (Fig. 2). This sequence of events, in which the curve of contraction becomes inverted with coronary occlusion and returns to the original upward inscription with release of occlusion, could be repeated several times in the same animal. Reproducibility of these changes was established in 15 animals, thereby demonstrating that the curve of contraction is extremely sensitive to the effects of ischemia resulting from coronary occlusion. Changes in the curve of contraction could therefore be used to indicate the presence of myocardial ischemia.

After occlusion of a major branch of the anterior descending coronary artery (Fig. 1), a central zone of ischemia was identified as the region in which fiber shortening was lost and replaced by the inverted curve of fiber lengthening. The intermediate zone of partial ischemia interposed between infarcted and noninfarcted myocardial regions was delineated as the region in which velocity of shortening was diminished by at least 50 percent of the control values. The stability of the curves of contraction in the intermediate zone was established 15 to 60 minutes after coronary occlusion.

Isoproterenol (0.25 to 0.5 μg/kg per min) was administered to eight animals. The means ± standard errors of changes in various indexes were as follows: Heart rate increased from an average of 113 ± 3 to 148 ± 4 beats/min ($P < 0.001$). Left ventricular systolic pressure increased from 108 ± 5 to 120 ± 5 mm Hg, whereas left ventricular end-diastolic pressure decreased. Before administration of isoproterenol, the velocity of shortening in the intermediate zone was 0.64 ± 0.05 mm/sec compared to the control value of 2.02 ± 0.16 mm/sec. This represented an average decline of 68 percent ($P < 0.001$) (Fig. 3). After administration, the velocity of shortening in the intermediate zone initially increased to 2.37 ± 0.09 mm/sec, representing an average increase of 270 per-

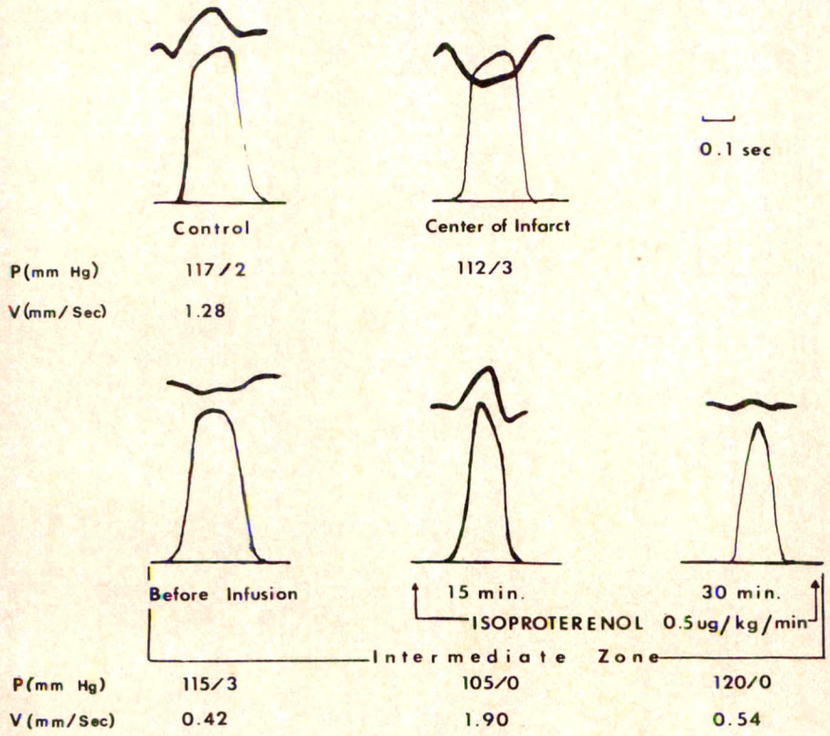

FIGURE 3. Effect of isoproterenol in eight dogs. An inverted curve of fiber lengthening is inscribed in the central zone (center of infarct). In the intermediate zone the curve of contraction shows a 67 percent decline in velocity of shortening (V) compared to the control value. Fifteen minutes after infusion of isoproterenol, velocity of shortening increased by 352 percent. At 30 minutes, a secondary reduction in velocity of shortening of 71 percent occurred, indicating a possible increase in the severity of ischemia in the intermediate zone.

cent (P <0.001). Such an increase in contractility persisted during the first 15 to 20 minutes of infusion. Thereafter, a secondary decline in velocity of shortening occurred in the test zone (Fig. 3). Thirty minutes after the onset of infusion, velocity of shortening decreased to 0.56 ± 0.02 mm/sec, a decline of 72 percent (P <0.001).

Norepinephrine was infused in a dose of 4.0 μg/min to eight animals (Fig. 4). Heart rate declined from 116 ± 2 to 104 ± 5 beats/min (P <0.01). Left ventricular systolic pressure increased from 110 ± 2 to 135 ± 3 mm Hg (P <0.005), whereas left ventricular end-diastolic pressure decreased. Before infusion of norepinephrine, velocity of shortening in the noninfarcted myocardium was 1.75 ± 0.12 mm/sec; in the intermediate zone it was 0.60 ± 0.02 mm/sec representing a decline of 66 percent (P <0.001) from the control level. After infusion, velocity of shortening in the intermediate zone increased to 1.47 ± 0.13 mm/sec, an increase of 145 percent (P <0.001). This increase in velocity of shortening persisted throughout the 60 minute observation period. Unlike isoproterenol, norepinephrine did not cause a secondary decline in contractility of the intermediate zone.

Ouabain (0.5 mg) was administered intravenously to eight animals. Sixty minutes after administration, heart rate decreased from 124 ± 2 to 119 ± 2 beats/min. Left ventricular systolic pressure did not change significantly, whereas left ventricular end-diastolic pressure decreased slightly. In the control state, velocity of shortening was 1.6 ± 0.04 mm/sec in the noninfarcted region and 0.60 ± 0.03 mm/sec in the intermediate zone, a reduction of 62 percent (P <0.01). Ouabain increased velocity of shortening in the intermediate zone to 1.21 ± 0.06 mm/sec, an increase of 84 percent (P <0.001) (Fig. 5).

Methoxamine (1 mg/min) was administered to eight animals. Within 5 minutes left ventricular systolic pressure increased from 118 ± 4 to 165 ± 2 mm Hg (P <0.001), whereas left ventricular end-diastolic pressure increased from 4 ± 2 to 12 ± 2 mm Hg (P <0.001). Heart rate decreased from 112 ± 3 to 96 ± 3 beats/min. In the control state, velocity of shortening in the intermediate zone measured 0.50 ± 0.02 mm/sec compared to 1.25 ± 0.02 mm/sec in the noninfarcted myocardial regions; this represents a reduction of 60 percent (P <0.001). Five minutes after administration of methoxamine there was loss of fiber shortening, which was replaced by fiber lengthening in the intermediate zone, as indicated by inversion of the systolic portion of the curve (Fig. 6). Such inversion of the curve indicates outward extension of the central zone of ischemia. In the noninfarcted region, velocity of shortening decreased to 0.65 ± 0.10 mm/sec (P <0.01).

Discussion

Apart from arrhythmias, infarct size appears to be the most important factor in determining the prognosis of patients with acute myocardial infarction.[15–17] During the early evolution of myocardial infarction, the size of the infarct is not fixed and may be altered.[8,9,18] Recent studies[8,12,19–21] have indicated that the severity and extent of ischemic injury may be modified by various physiologic and pharmacologic interventions.

The ability to modify infarct size is essentially dependent on the presence of ischemic but nonnecrosed

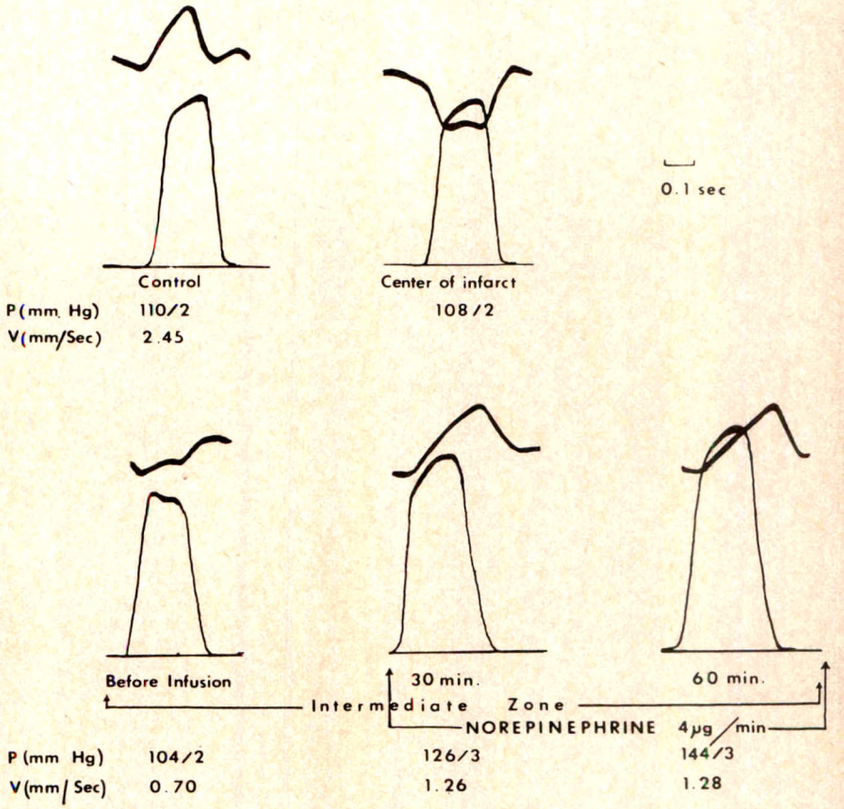

FIGURE 4. Effect of norepinephrine in eight dogs. The intermediate zone showed a 71 percent reduction in velocity of shortening compared to the control level. After infusion of norepinephrine, velocity of shortening increased by 80 percent at 30 minutes and 82 percent at 60 minutes. There was no secondary decline in contractility.

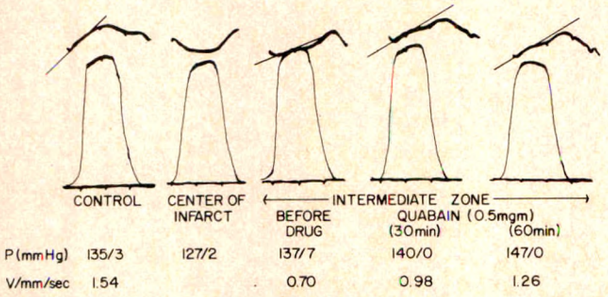

FIGURE 5. Effect of ouabain in eight dogs. In the intermediate zone velocity of shortening was 56 percent of the control value. Ouabain resulted in an increase in velocity of shortening of 25 percent at 30 minutes and 80 percent at 60 minutes. There was no secondary decline in contractility.

viable myocardial cells within the area of reversible ischemic injury.[18,22] These cells constitute the twilight or intermediate zone bordering the infarcted myocardium. The ultimate fate of an ischemic myocardial cell is determined by several factors. With a mild degree of anoxia anaerobic glycolysis may occur and the myocardium may recover uneventfully.[22,23] When ischemia is more severe, changes may occur in the mitochondria and reticulum. However, recovery is possible as long as nuclei and cell membranes are intact.[22,24] The severity of ischemic injury is also determined by the state of the cells before injury, the level of endogenous glycogen stores, substrate availability[25] and cellular environmental factors such as pH and ionic concentration.[22,23]

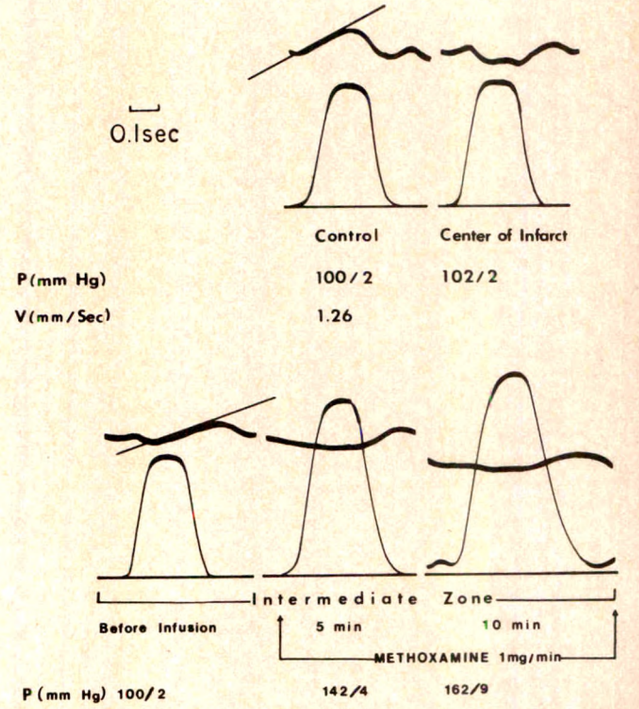

FIGURE 6. Effect of methoxamine in eight dogs. The intermediate zone showed a 55 percent decline in velocity of shortening compared to the control value. After infusion of methoxamine, the curve became inverted, indicating loss of fiber shortening and its replacement by passive fiber lengthening. Loss of contractility in the intermediate zone suggests extension of the central zone.

In this study, infarct size was delineated by means of a strain gauge-tipped catheter probe that measures myocardial fiber shortening.[4,13] The probe records curves of myocardial contraction over localized segments of ventricular wall[4,14]; these curves of contractility are extremely sensitive to the effect of ischemia.[4,8,14,26] After coronary occlusion, contractility immediately declines and the failure of contraction is complete within 15 to 30 seconds (Fig. 2). Inability to contract is associated with passive distension (fiber lengthening) as ischemic myocardium yields to intraventricular pressure.[27] This is reflected in the inversion or downward inscription of the curve in systole. If coronary occlusion is released and flow restored at any time within 45 minutes, myocardial contraction returns and the curve is restored to its original upward inscription (Fig. 2). This sequence of events is reproducible. The catheter probe can therefore be used to distinguish between the noncontracting central zone of complete ischemia and nonischemic myocardium on the basis of the direction in which the curve is inscribed in systole. The intermediate zone of partial ischemia that lies between infarcted and noninfarcted myocardium was defined as the region in which contractility was diminished but not completely lost (Fig. 1). Changes in contractility of the intermediate zone could therefore be used to evaluate the effect of cardiotonic drugs on the severity of ischemia. Thus, if a cardiac drug increases myocardial oxygen consumption in excess of oxygen delivery, then the resulting negative oxygen balance will lead to an increase in the degree of ischemia that, in the intermediate zone, will be reflected as an additional decline in contractility.

The positive inotropic action of the cardiac stimulating drugs examined in our study—isoproterenol, norepinephrine and ouabain—initially augmented contractility of myocardial fibers in the intermediate zone, as indicated by increased velocity of shortening (Fig. 3 to 5). This effect was similar to that observed in the noninfarcted region. An increase in contractility of partially ischemic cells implies a concomitant increase in oxygen supply since enhanced contractility increases oxygen consumption.[6] But during the 30 to 60 minute observation periods it became evident that these drugs had dissimilar effects.

Isoproterenol

Continuous infusion of isoproterenol resulted in a secondary decline in contractility of the intermediate zone which became noticeable at 30 to 45 minutes (Fig. 3). The positive inotropic action of the drug was not diminished at this time, as was evident from changes in the nonischemic region. It is therefore reasonable to assume that the decline in contractility of the intermediate zone, despite the continued positive inotropic action of the drug, reflects an increase in the severity of ischemia of cells in this region.[28] This increase may be due to either or both a progressive augmentation of oxygen consumption or decrease in oxygen supply due to decline in collateral flow or diminished coronary perfusion.[29] The increase in heart rate that accompanied isoproterenol action also has an effect of increasing myocardial oxygen consumption.[30] Other possible mechanisms are a direct effect whereby isoproterenol in large doses produces myocardial necrosis.[31] This effect is unlikely with the doses used in our study. Increased lactate production by the drug may be a factor in depressing myocardial contractility.[32] Maroko et al.[9] reported that the additional myocardial sites showing S–T segment elevation after isoproterenol infusion also showed depression of myocardial creatine phosphokinase, and they attributed this finding to an increment in cell death. Such actions of isoproterenol on the myocardium of the intermediate zone will have the effect of extending the size of the infarct.

Norepinephrine

Norepinephrine did not result in a secondary decline in contractility of the intermediate zone (Fig. 4). The hemodynamic effects of this drug differed from those of isoproterenol since there was an increase in arterial pressure thereby insuring adequate coronary perfusion.[33,34] Further, the decrease in heart rate permits an adequate diastolic filling period with its beneficial effect on cardiac output and coronary perfusion.[35] Because of these actions of the drug, the increase in oxygen supply apparently kept pace with the increased myocardial oxygen consumption. These findings are consistent with the observations of Sayen et al.[10] who reported that levarterenol results in an apparent shrinkage of the regionally ischemic myocardium. The difference in the effects of isoproterenol and norepinephrine on the severity of myocardial ischemia is also supported by the studies of Furuse et al.,[28] who measured myocardial PO_2 and PCO_2 by means of a mass spectrometer. They concluded that in the presence of coronary stenosis, isoproterenol failed to increase coronary flow enough to offset increased oxygen consumption and resulted in a marked reduction in myocardial PO_2 and increase in PCO_2. By contrast, norepinephrine led to an increase in coronary flow, augmentation of PO_2 and a decrease in PCO_2.

Ouabain

Ouabain augmented contractility of the intermediate zone, and this effect persisted during the 60 minute observation period (Fig. 5). Unlike isoproterenol, ouabain did not produce a secondary decline in contractility. It is assumed therefore that digitalis does not induce a negative oxygen balance and consequently in situations comparable to our experiments may not have the effect of extending infarct size. The net effect of digitalis on myocardial oxygen consumption is determined by at least two opposing factors.[36] In a failing heart it has an oxygen-sparing effect through its action in reducing myocardial wall tension. Further, by improving performance of the fail-

ing ventricle it may increase coronary flow and, hence, oxygen delivery. An increase in myocardial contractility ($\dot{V}_{max}$) has the opposite effect of increasing oxygen consumption; in a nonfailing heart this becomes the dominant effect of digitalis.

Methoxamine

Methoxamine led to inversion of the curve of contractility in the intermediate zone; that is, it resulted in loss of fiber shortening and its replacement by passive fiber lengthening (Fig. 6). Methoxamine stimulates alpha adrenergic receptors, resulting in vasoconstriction. The increase in arterial pressure may increase coronary perfusion.[33] At the same time the increase in left ventricular afterload and, hence, myocardial wall tension increases myocardial oxygen consumption. The increase in oxygen demand was apparently greater than that which could be offset by the possible improved coronary perfusion. This led to worsening of the severity of ischemia in the intermediate zone. A marked increase in afterload may therefore extend the size of myocardial infarction. These findings are in contrast to the conclusions of Maroko et al.,[9] who reported that methoxamine results in a decrease in the extent of ischemic injury.

Clinical Implications

Although one must be cautious in extrapolating the results of canine experiments to man, our observations have important clinical implications. Among cardiac stimulating drugs used in the treatment of pump failure in acute myocardial infarction, isoproterenol seems most likely to induce negative oxygen balance of a magnitude that may further reduce the already impaired contractility of partially ischemic myocardial fibers. This will have the effect of extending the nonfunctioning zone of ischemia. Norepinephrine and digitalis, when administered in doses comparable to those used in our study, are not likely to exert such deleterious effects. An excessive increase in left ventricular afterload such as that induced by methoxamine may result in extension of infarct. An increase in the noncontracting ischemic myocardium is likely to accentuate cardiac dysfunction and thereby set up a vicious cycle of decreasing coronary flow and enlarging infarct size.

Acknowledgment

I thank Ralph Williams and H. S. Buttar for technical assistance.

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Pathophysiology of Tachycardia- and Bradycardia-Dependent Block in the Canine Proximal His-Purkinje System After Acute Myocardial Ischemia

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An experimental model for the study of conduction disturbances in the proximal His-Purkinje system after acute myocardial ischemia was produced in 24 dogs by ligation of the anterior septal artery. Eighteen of the 19 dogs that survived the initial vulnerable arrhythmic period showed different degrees of conduction disturbance in the bundle of His, right and left bundles or any combination thereof usually within 1 to 2 1/2 hours after ligation. In 14 experiments normal conduction was restored within 8 hours. In all cases with bundle branch block, the block was initially demonstrated on increasing or slowing the heart rate, with a range of intermediate rates at which conduction was normal. Within 45 minutes the block became constant at all heart rates, but within 2 to 6 hours was again replaced by normal conduction at intermediate rates and, finally, consistent normal conduction. In 12 experiments showing intra-His bundle block (always demonstrated by splitting of the His potential into two deflections, Hb_1 and Hb_2) increasing the rate resulted in second or third degree block with the blocked impulse localized between the two deflections. In 5 of 12 experiments, slowing the rate gave rise to first degree intra-His bundle block (lengthening of the Hb_1–Hb_2 interval).

Our in vitro observations suggested that the initial phase of tachycardia- and bradycardia-dependent block in the proximal His-Purkinje system can be explained by characteristic changes in the electrophysiologic properties of two groups of Purkinje fibers which may be due to differential localization of metabolites released in the ischemic zone. Tachycardia-dependent block was based on a time-dependent response of Purkinje fibers partially depolarized by an increase in extracellular concentration of potassium ion. Bradycardia-dependent block was explained by a slight to moderate decrease of resting potential, a normal slope of phase-4 depolarization and reduced membrane responsiveness associated with shift of the threshold potential toward zero. Contrary to previous data, our findings indicate no relation between enhanced automaticity of pacemaker cells and bradycardia-dependent conduction disturbances.

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The majority of cases of intermittent bundle branch block are rate-dependent, and the conduction disturbance is usually associated with either acceleration of the heart rate (tachycardia-dependent block) or slowing of the rate (bradycardia-dependent block).[1] Tachycardia-dependent bundle branch block at short cycle lengths is readily explained by impulse spread through incompletely repolarized fibers because of the time necessary for the physiochemical processes of re-

TABLE I

Conduction Disturbances in the Canine Proximal His-Purkinje System (HPS) After Ligation of the Anterior Septal Artery in 18 Experiments

Experiment	Nature of Block in Proximal His-Purkinje System						Type of A–V Block			Time Course of Block (hours)	
	Bundle of His		Right Bundle		Left Bundle						
	TD	BD	TD	BD	TD	BD	1°	2°	3°	Onset	Duration
1	−	−	+	+	−	−	−	−	−	1.30	5.30
2	−	−	+	+	−	−	−	−	−	1.45	26
3	+	−	−	−	−	−	+	+	+	2.10	4.20
4	+	+	−	−	−	−	+	+	+	1.40	2.15
5	+	+	−	−	−	−	+	+	+	1.05	2.05
6	+	+	−	−	−	−	+	+	+	1.30	3.20
7	+	−	−	−	−	−	+	−	−	1.20	4.50
8	+	−	+	+	−	−	+	+	+	2.10	4.10
9	+	−	+*	+*	−	−	+	+	+	1.50	24
10	+	+	+	+	−	−	+	+	−	1.00	7 days
11	+	−	+	+	−	−	+	+	+	1.30	46
12	+	+	+	+	+	−	+	+	+	1.50	5.20
13	+	−	+	+	+	+	+	+	+	2.20	4.20
14	+	−	+*	−	+	+	+	+	+	1.40	2.40
15	−	−	+	+	+	−	+	+	+	1.20	5.40
16	−	−	+	−	+	+	+	+	+	1.50	4.10
17	−	−	+*	+	+	−	+	+	+	1.40	4.40†
18	−	−	+	−	+	+	+	+	+	1.10	3.50†

*Incomplete bundle branch block.
†Died of ventricular fibrillation.
A–V = atrioventricular; BD = bradycardia-dependent; TD = tachycardia-dependent.

covery.[2] Tachycardia-dependent block at heart rates usually associated with normal intraventricular conduction is considered pathologic and is conventionally ascribed to abnormal prolongation of the functional refractory period of the conduction system; however, the underlying electrophysiologic mechanisms have not been precisely delineated. Bradycardia-dependent bundle branch block is the subject of a good deal of speculation. Although several mechanisms have been proposed, bradycardia-dependent block has recently been attributed to enhanced phase-4 depolarization in the bundle branch system.[1,3,4] This explanation represents an extrapolation of the observations of Singer et al.[5] on the behavior of isolated Purkinje fibers made abnormal by various pathophysiologic interventions. Both tachycardia- and bradycardia-dependent block may occur in the same bundle branch system.[1,3,6] We have shown by deductive analysis of clinical records that repetitive block of the impulse in one part of the bundle branch system (the posterior division of the left bundle) can be explained by the concomitant operation of a tachycardia- and a bradycardia-dependent block.[7] Recently, critical observations of the onset and course of transient bundle branch block with acute myocardial infarction in man revealed several examples of rate-dependent bundle branch block showing both tachycardia- and bradycardia-dependent block and normal intraventricular conduction at intermediate heart rates.[8,9]

These observations stimulated the production of an appropriate experimental model for the study of the onset and course of transient bundle branch blocks after ligation of the anterior septal artery in dogs. Bundle branch block during both rapid and slow heart rates with normal conduction at intermediate rates was observed at the onset and before the termination of the transient conduction abnormality. In addition, the behavior of the bundle of His was usually similar to that of the bundle branches showing both tachycardia- and bradycardia-dependent blocks. Our in vitro observations revealing characteristic changes in the Purkinje fibers involved in the acute ischemic process are highly relevant to the in vivo observations. This report describes the in vivo study with reference to the in vitro observations. A complete report of the latter will appear in a separate communication.

Material and Methods

Twenty-four mongrel dogs weighing 10 to 20 kg were anesthetized with intravenously administered sodium pentobarbital (30 mg/kg). The animals were intubated and placed on a mechanical respirator. Blood pressure in the right femoral artery was monitored through a polyethylene catheter connected to a Statham transducer. A thoracotomy was made through the fourth left intercostal space. The bifurcation of the left coronary artery was exposed by retracting the tip of the left atrial appendage and incising the epicardium overlying the proximal portions of the anterior descending and left circumflex arteries. The anterior septal

artery was exposed by blunt dissection of the bifurcation and branches of the left coronary artery and a ligature was loosely passed around the vessel. Recordings of electrocardiographic leads II and aVR toegether with catheter electrode recordings from the bundle of His and right and left bundle branches were obtained.[10–12] Accuracy of the His and bundle branch potentials was validated by pacing from the corresponding sites together with analysis of the temporal relations of these potentials to the V deflection (25 to 35 msec for the His bundle deflection, 15 to 20 msec for the proximal right and left bundle potentials and 5 to 15 msec for recording of the electrical activity of the distal bundle branches). Atrial pacing was performed with use of a bipolar plunge wire electrode inserted at the left atrial appendage, a Grass S88 stimulator and stimulus isolation unit. Vagally induced slowing or cardiac arrest was accomplished by delivery of a 0.05 msec square wave pulse of 1 to 10 volts intensity at a frequency of 20 Hz to the left or right cervical vagosympathetic trunk. All records were made on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-8) at a paper speed of 25 to 200 mm/sec with the filter frequencies of 0.1 to 200 cycles/sec for electrocardiographic leads and 40 to 200 cycles/sec for electrographic recordings.

Control records during sinus rhythm, vagally induced cardiac slowing and atrial pacing up to rates that produced atrioventricular (A–V) Wenckebach conduction were obtained in each experiment before ligation of the anterior septal artery. The recorded electrical activity was then monitored for intervals of up to 12 hours after ligation. The effects of both cardiac acceleration and slowing were frequently tested throughout the experiment. In five dogs, after completion of the initial study, the thoracotomy incision was closed and the dogs were followed up for intervals of up to 7 days. Several dogs were sacrificed and their hearts used for in vitro studies performed by conventional microelectrode technique.[13] In all experiments postmortem dissection was performed to verify that the anterior septal artery had been ligated.

Results

Thirty seconds to 1 minute after ligation of the anterior septal artery, ST–T wave changes were observed in the surface electrocardiographic leads. A few minutes later, there was enhanced ventricular activity in the form of single or multiple closely coupled ectopic beats that usually reached a maximum after 15 to 20 minutes and subsided within 30 minutes. The initial burst of ectopic activity was followed by a quiescent period of 6 to 12 hours succeeded by a second surge of multifocal ventricular rhythm lasting several days. In spite of careful attention to the initial vulnerable arrhythmic period, five dogs died of ventricular fibrillation in the first 30 minutes after ligation. In two other dogs ventricular fibrillation developed 5 to 6 hours later. These dogs had complete A–V dissociation due to bilateral bundle branch block and an idioventricular escape rhythm. All the remaining dogs were sacrificed at intervals ranging from 6 hours to 7 days after ligation. Only one dog had no evidence of conduction disturbance at the proximal His-Purkinje system during 8 hours of observation. All other 18 dogs that survived the early vulnerable arrhythmic period showed various degrees of conduction disturbances at the level of the His bundle, right and left branches or any combination thereof (Table I).

Disturbances of conduction at the proximal His-Purkinje system usually appeared 100 minutes after ligation and were maximal 2 to 4 hours after ligation. In 14 experiments normal conduction was regained within 8 hours. In all cases showing bundle branch block, the block was initially demonstrated during rapid heart rates (tachycardia-dependent) or slow rates (bradycardia-dependent) with a phase of normal intraventricular conduction or incomplete bundle branch block at intermediate heart rates. The phase of normal conduction or incomplete block gradually disappeared, and block became constant at all rates. In some experiments stable block occurred within a few minutes; in others the intermittent conduction disturbance could be demonstrated for 15 to 45 minutes. Usually bradycardia-dependent bundle branch block could not be demonstrated until either a tachycardia-dependent block or an incomplete block at intermediate heart rates had appeared. In all but one case in which the bundle branch block was transient, normal intraventricular conduction at an intermediate heart rate with bundle branch block on increasing or decreasing the rate was again observed. The range of heart rates at which normal conduction occurred gradually increased until conduction was

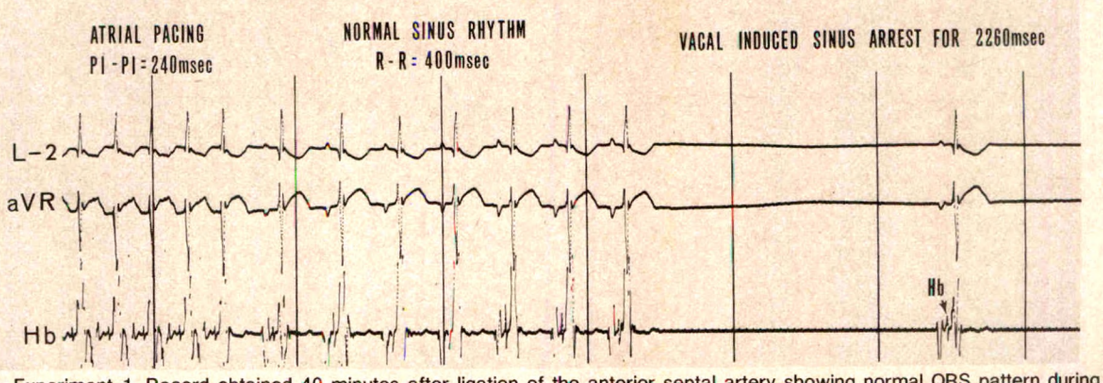

FIGURE 1. Experiment 1. Record obtained 40 minutes after ligation of the anterior septal artery showing normal QRS pattern during normal sinus rhythm, atrial pacing and a vagally induced sinus arrest for 2,260 msec. Hb represents the His bundle electrogram. Time lines in this and subsequent figures are at 1 second intervals.

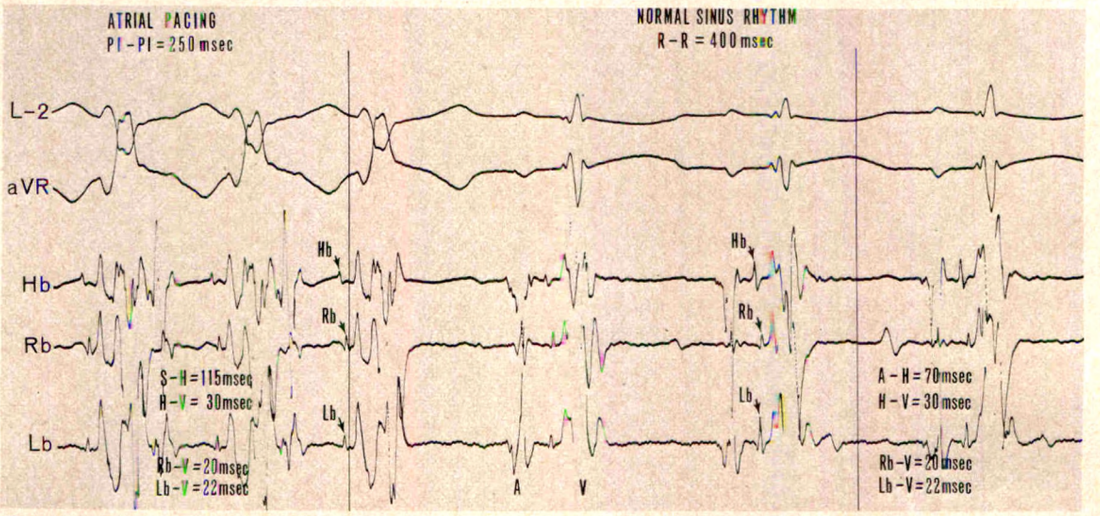

FIGURE 2. Experiment 1. Record obtained 90 minutes after ligation of the anterior septal artery showing a tachycardia-dependent right bundle branch block during atrial pacing. In this and subsequent records, Hb, Rb and Lb are the electrograms recorded from the bundle of His and right and left bundles, respectively, and A and V represent the atrial and ventricular deflections.

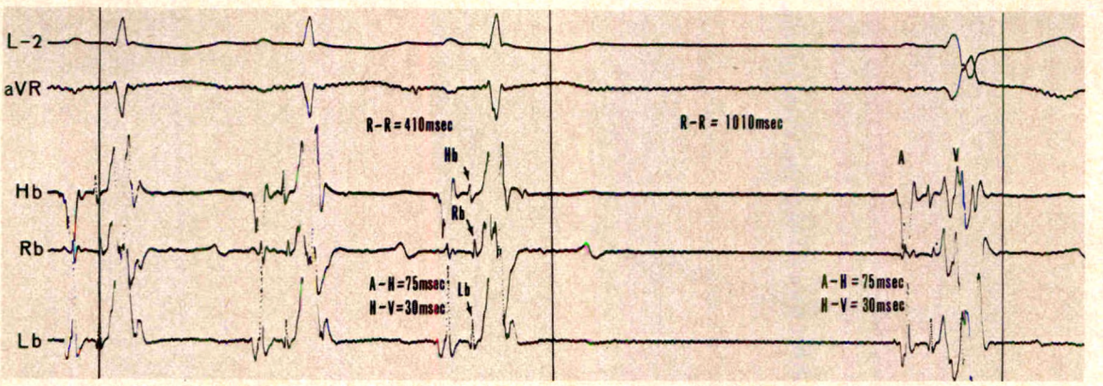

FIGURE 3. Experiment 1. Record obtained 2 minutes after Figure 2 illustrating a bradycardia-dependent right bundle branch block.

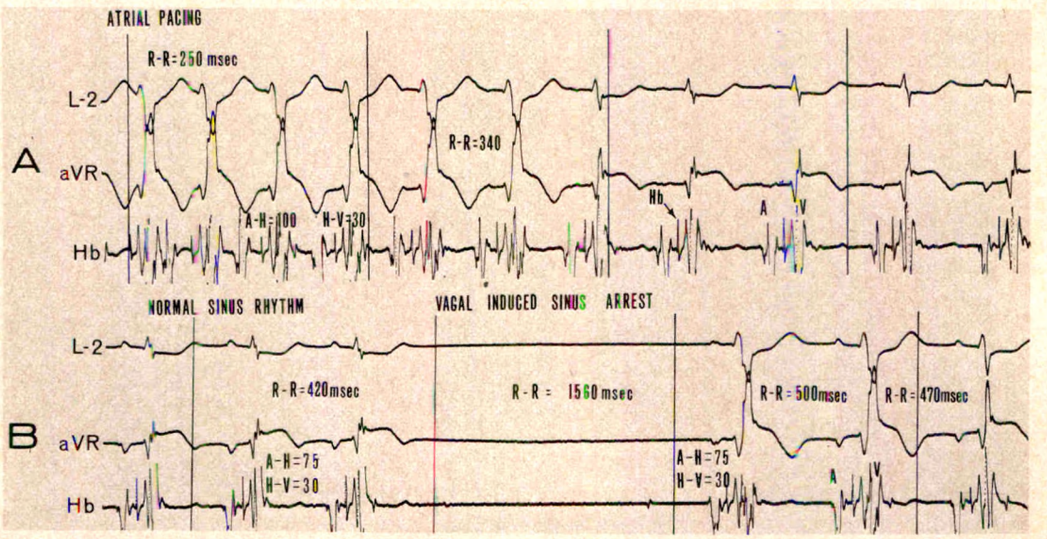

FIGURE 4. Experiment 1. Records A and B are continuous and were obtained 102 minutes after ligation of the anterior septal artery. They illustrate incomplete right bundle branch block at intermediate heart rate with tachycardia- and bradycardia-dependent complete block on increasing or slowing the rate to critical cycle lengths of 340 and 470 msec, respectively.

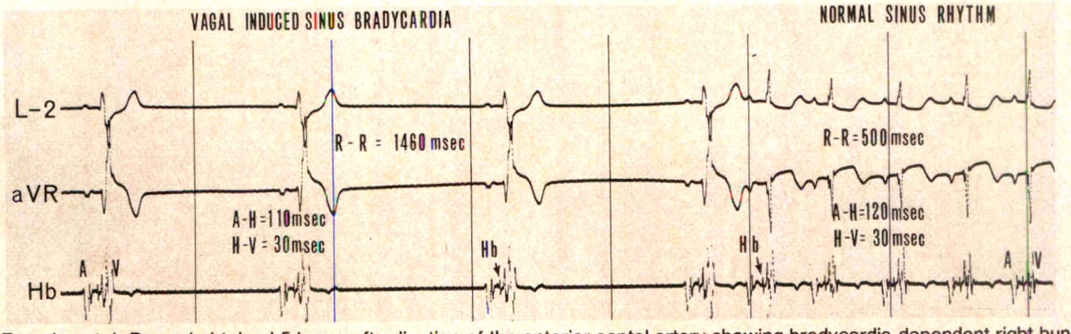

FIGURE 5. Experiment 1. Record obtained 5 hours after ligation of the anterior septal artery showing bradycardia-dependent right bundle branch block during vagally induced sinus bradycardia. Release of the vagal effect resulted in prompt return of sinus rhythm and normal intraventricular conduction.

consistently normal. In all cases showing intra-His bundle block, the bundle of His potential was fractionated into two (sometimes more) deflections termed Hb_1 and Hb_2. These cases responded to tachycardia by the development of first, second or third degree A–V block that was always localized between the Hb_1 and Hb_2 deflections. Response to bradycardia was demonstrated in only five experiments and always in the form of first degree block (an increase of the Hb_1–Hb_2 interval).

Selected examples illustrating the pertinent electrophysiologic changes in the proximal His-Purkinje system after ligation of the anterior septal artery are given below.

Experiment 1

Figure 1 was obtained 40 minutes after ligation of the anterior septal artery. The QRS configuration in leads II and aVR is the same as in the control records with the exception of the ST–T changes that usually develop within the first few minutes after ligation. The QRS configurations and H–V intervals are the same during normal sinus rhythm at a rate of 150/min, atrial pacing at a rate of 250/min and after a vagally-induced bradycardic interval of 2,260 msec (rate 26/min). These findings demonstrate that there are no tachycardia- or bradycardia-dependent conduction disturbances in the proximal His-Purkinje system at these rates.

Figure 2, obtained 90 minutes after ligation, illustrates a tachycardia-dependent complete right bundle branch block with atrial pacing at a rate of 240/min (the first three beats). Normal intraventricular conduction is still present during normal sinus rhythm at a rate of 150/min (last three beats). During the rapid rate, the A–H interval lengthens, which is a normal physiologic response of conduction in the A–V node. The H–V, Rb–V and Lb–V intervals remain unchanged during both normal intraventricular conduction and right bundle branch block. These findings suggest that during right bundle branch block, the maximal delay or block of impulse conduction in the right bundle branch sys-

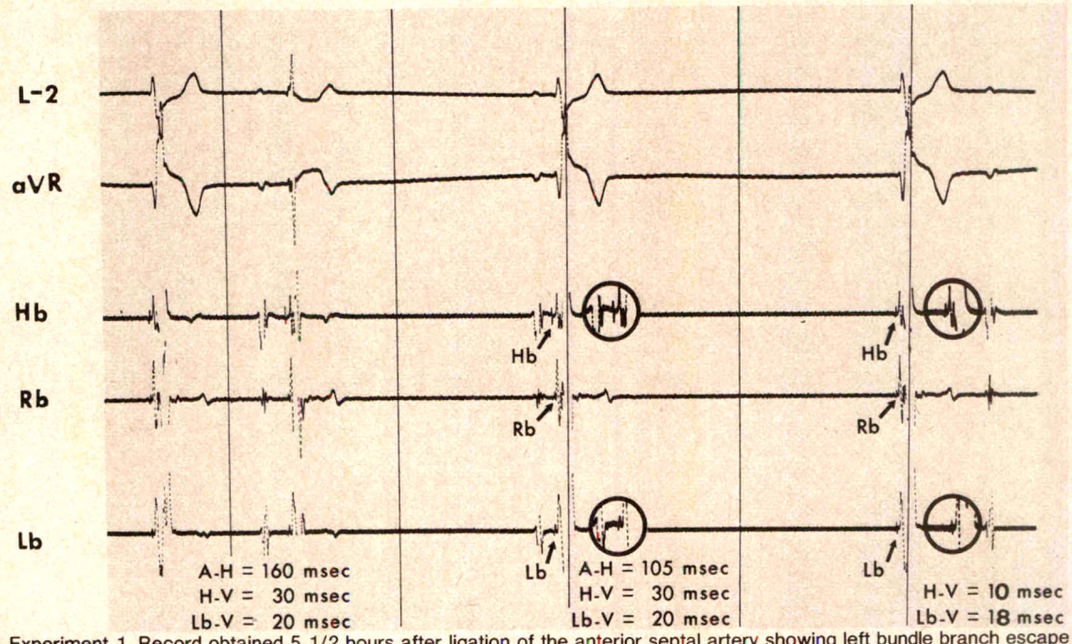

FIGURE 6. Experiment 1. Record obtained 5 1/2 hours after ligation of the anterior septal artery showing left bundle branch escape beats (first and fourth beats) and supraventricular capture beats (second and third beats). Bradycardia-dependent right bundle branch block is present with exactly the same QRS configuration both in the late supraventricular capture beat and the left bundle branch escape beats. Retrograde activation of the His bundle occurs during the escape beats and the H–V interval is short.

tem occurs below the recording site of the proximal right bundle potential.

Figure 3, obtained 2 minutes after Figure 2, illustrates a bradycardia-dependent right bundle branch block. During this block, the conduction delay in the right bundle branch system is again located distal to the recording site of the proximal right bundle branch potential.

Figure 4, obtained 10 minutes later, shows incomplete right bundle branch block during normal sinus rhythm and complete block developing on increasing or slowing the heart rate. The critical R–R cycles for tachycardia- and bradycardia-dependent complete block are 340 and 470 msec, respectively. Three minutes after this figure was recorded, complete right bundle branch block was constantly observed at all heart rates. This stable block remained for another 2 1/2 hours (4.15 hours after ligation) when normal intraventricular conduction was again observed at an intermediate heart rate with right bundle branch block elicited on increasing or slowing the rate.

Figure 5, obtained 5 hours after ligation, shows complete right bundle branch block during vagally induced sinus bradycardia at a rate of 41 beats/min. Sudden release of the vagal effect (right half of this figure) results in a prompt return of sinus rhythm at a rate of 120/min and normal intraventricular conduction. Increase of the heart rate to 240/min (not shown in the figure) induced a tachycardia-dependent right bundle branch block.

Figure 6 was obtained 5 1/2 hours after ligation. Vagally induced cardiac slowing reveals a regular escape rhythm arising from the left ventricle at an average rate of 30/min. The left ventricular escape beats (first and fourth beats) are preceded by a left bundle branch potential, thus suggesting that the beats originate in the proximal left bundle branch system. There is retrograde activation of the bundle of His and the H–V interval is short. The second and third beats in this figure are conducted sinus beats (capture beats). The second beat inscribed after an R–R interval of 690 msec conducts normally in the right bundle branch system; the third beat, occurring after a longer R–R interval of 1,580 msec, shows a right bundle branch block pattern. These findings indicate the presence of a bradycardia-dependent right bundle branch block. The configuration of the slow escape beats arising from the proximal left bundle branch system is exactly the same as that of conducted sinus beats with bradycardia-dependent right bundle branch block.

Figure 7 was obtained 6 1/2 hours after ligation. With vagally induced cardiac slowing, a regular right ventricular escape rhythm begins to occur at a relatively faster rate than that of the left ventricular rhythm (48/min) (last three beats). The escape beats are not preceded by a right bundle branch potential, thus suggesting that the beats originate distally in the right ventricular Purkinje system. Sinus tachycardia, present during the first three beats in this figure, is followed by vagally induced sinus slowing. The fourth and fifth beats represent conducted sinus impulses at cardiac cycle lengths longer than the escape cycle length. Bradycardia-dependent right bundle branch block is not present in these beats. Seven hours after ligation tachycardia-dependent bundle branch block was no longer observed.

Experiment 10

*Figure 8*A shows basal recordings, including the right bundle branch potential, before ligation of the anterior septal artery. In Figure 8B, obtained 60 minutes after ligation, the His bundle potential has clearly split into two deflections (Hb_1 and Hb_2) with only slight prolongation of the Hb_1–V interval. Panels C and D show pacing from the proximal and distal His deflections giving rise to stimulus to V intervals of 35 and 25 msec, respectively, which are equal to the Hb_1–V and Hb_2–V intervals in B.

Figure 9 was obtained 125 minutes after ligation. The conventional electrocardiographic leads show a constant degree of incomplete right bundle branch block at an intermediate heart rate (last two beats). Increasing the heart rate to 214/min (first two beats) leads to complete right bundle branch block during which the right bundle branch potential is not seen. This may be due to marked delay in the inscription of the potential which moves toward and becomes buried in the large V deflection or to a complete block of conduction proximal to the recording site. The former explanation is probably true as shown by the gradual movement of the right bundle branch potential outside the V deflection to its original position before this deflection on termination of atrial pacing. There is an associated but

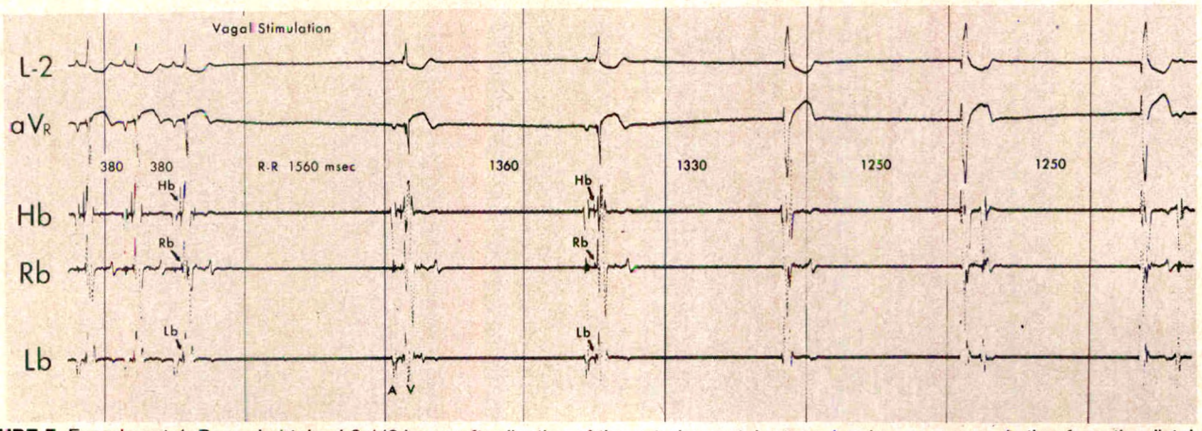

FIGURE 7. Experiment 1. Record obtained 6 1/2 hours after ligation of the anterior septal artery showing an escape rhythm from the distal right ventricular Purkinje system. Bradycardia-dependent right bundle branch block is absent in the fourth and fifth beats after cardiac cycle lengths longer than that of the escape cycle.

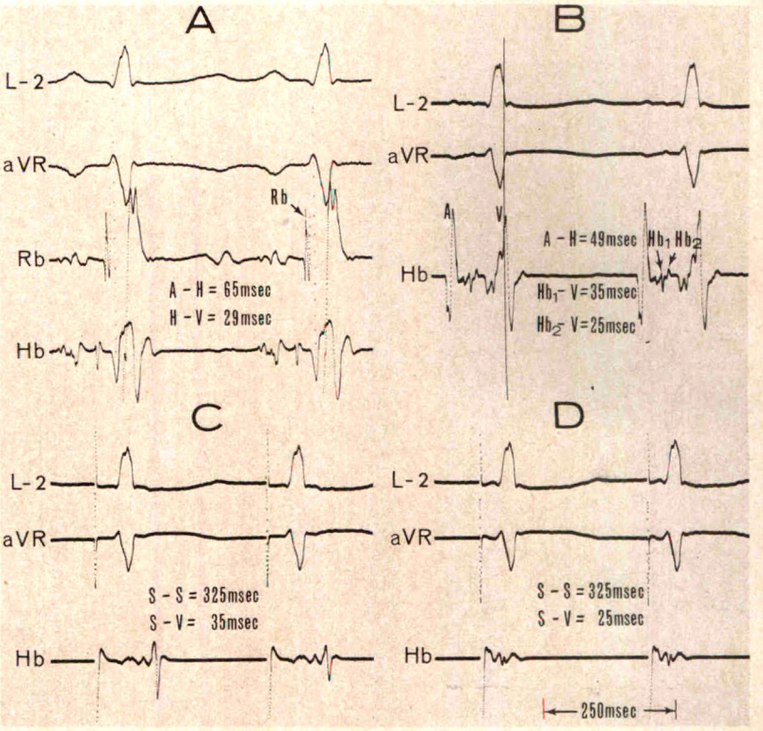

FIGURE 8. Experiment 10. **A,** control record obtained before ligation of the anterior septal artery. **B,** record obtained 60 minutes later illustrating splitting of the His potential into two deflections (Hb_1 and Hb_2) with slight lengthening of the H–V interval. Panels **C** and **D** represent His bundle pacing from the proximal and distal His deflections, respectively.

much less perceptible change in the pattern of incomplete right bundle branch block in the conventional leads. This figure thus illustrates a tachycardia-dependent complete right bundle branch block disturbance in the proximal right bundle branch system superimposed on a pattern of incomplete right bundle branch block due to the development of a constant degree of conduction delay in the right bundle. During the rapid heart rate, the H–V interval is slightly prolonged (from 33 to 39 msec) mainly as a result of a slight prolongation in the Hb_1–Hb_2 interval.

Figure 10, recorded 10 minutes later during constant atrial pacing at a slightly faster rate of 235/min, shows this phenomenon more clearly. Several spontaneous transitions from 1:1 A–V conduction to 2:1 A–V block and vice versa are observed with the block localized in the His bundle between the Hb_1 and Hb_2 deflections. Critical analysis of the H–V intervals during 1:1 A–V conduction showed a minimal increment of 5 to 10 msec before the blocked P wave which is mainly occurring between the Hb_1 and Hb_2 deflections (magnified sections). This arrangement reflects the presence of a Wenckebach type of conduction in the His bundle with an increment of only a few milliseconds.[14,15]

Figure 11, recorded 2 minutes after Figure 10, shows the effect of vagally induced cardiac slowing for 2,150 msec (rate 28 beats/min). A bradycardia-dependent complete right bundle branch block developed with disappearance of the Rb potential in the first conducted sinus impulse after the long pause. The H–V interval is significantly prolonged

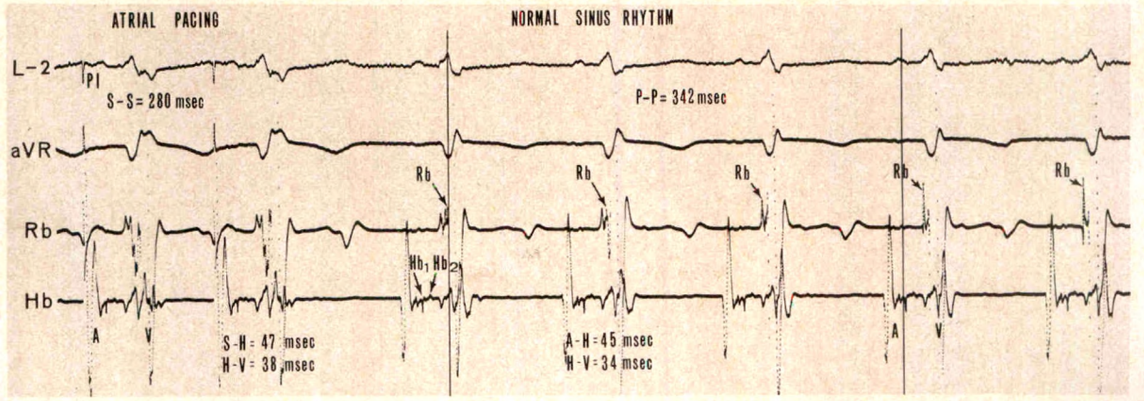

FIGURE 9. Experiment 10. Record obtained 125 minutes after ligation of the anterior septal artery showing incomplete right bundle branch block during normal sinus rhythm with a tachycardia-dependent complete block on atrial pacing. Note gradual movement of the right bundle potential (Rb) outside the V deflection after termination of pacing.

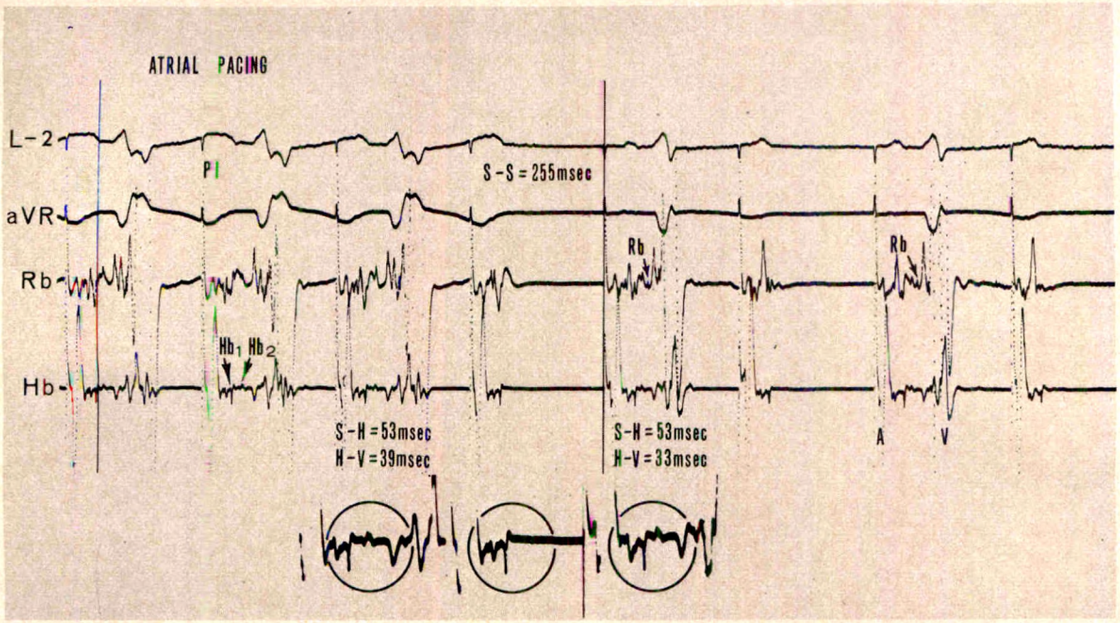

FIGURE 10. Experiment 10. Record obtained 135 minutes after ligation of the anterior septal artery showing constant atrial pacing at a rate of 235 beats/min. Note transition from 1:1 A–V conduction to 2:1 A–V block with the block localized in the bundle of His between the HB_1 and Hb_2 deflections. There is a Wenckebach arrangement with an increment of a few msec.

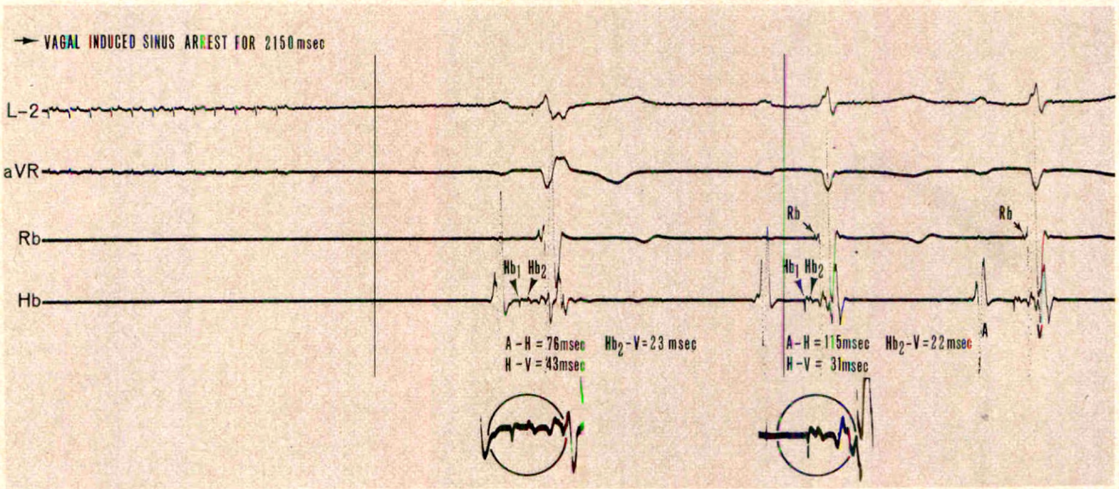

FIGURE 11. Experiment 10. Record obtained 2 minutes after Figure 10 showing a concomitant bradycardia-dependent first degree intra-His bundle block and complete right bundle branch block.

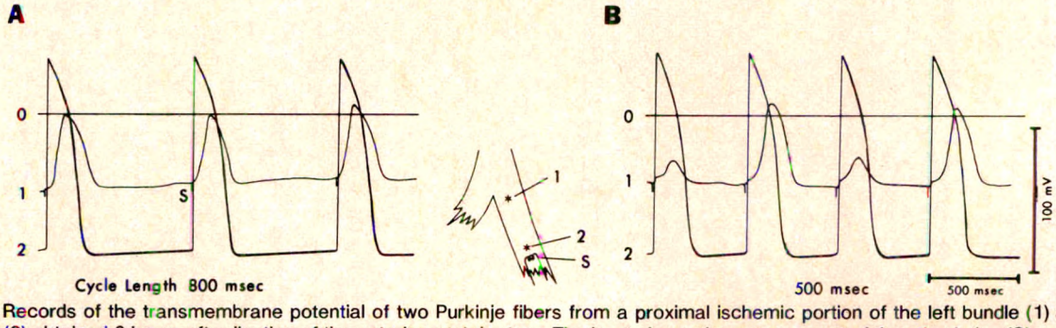

FIGURE 12. Records of the transmembrane potential of two Purkinje fibers from a proximal ischemic portion of the left bundle (1) and a distal normal zone (2) obtained 6 hours after ligation of the anterior septal artery. The inset shows the arrangement of the stimulating (S) and recording electrodes. In **A**, the proximal fiber has a low resting potential and a slowly rising action potential of small amplitude. In **B** there is a 2:1 time-dependent response of this fiber to an increase in the driving frequency. Although there is alternation of action potential amplitude, a significant conduction delay or block would be present in every cycle.

mainly because of lengthening of the Hb_1–Hb_2 interval (magnified sections). Figure 11 thus illustrates a bradycardia-dependent conduction disturbance in both the bundle of His and the right bundle branch system.

Critical analysis of Figures 10 and 11 reveals that 120 minutes after ligation of the anterior septal artery, a constant slight degree of conduction delay developed at both the bundle of His and the right bundle branch at intermediate heart rates. A tachycardia-dependent complete block at both sites could be elicited by atrial pacing. A bradycardia-dependent first degree intra-His bundle block and complete right bundle branch block could be illustrated by vagally induced cardiac slowing. A follow-up study for 7 days revealed complete correction of the intra-His bundle conduction disturbance but persistence of a tachycardia- and bradycardia-dependent right bundle branch block.

Discussion

General Considerations

Study of the onset and course of acute ischemic conduction disturbances in the canine proximal His-Purkinje system has shown the concomitant development of tachycardia- and bradycardia-dependent intermittent block both at the onset and before the termination of the transient conduction abnormality. The same electrophysiologic disturbance has been recently demonstrated in man.[8,9] The observation of tachycardia- and bradycardia-dependent bundle branch block several days after the ligation of the anterior septal artery in dogs and in some patients several months after the acute ischemic episode[8,9] suggests that this phenomenon is probably related to the electrophysiologic disturbances underlying intermittent conduction disorders in the His-Purkinje system in general. These disorders tend to occur at both rapid and slow heart rates with normal conduction at intermediate rates.

Our observations after ligation of the anterior septal artery in dogs strongly suggest that the experimental model is appropriate for study of conduction disturbances in the proximal His-Purkinje system after acute myocardial ischemia. The anatomic distribution of the His-Purkinje system in dogs and the canine blood supply are sufficiently similar to those of man to make the dog a suitable experimental animal. Direct extrapolation of the results of animal observations to the man should be made cautiously because the distribution of the septal arteries differs in the two species[16] and because in man lesions of the conduction system frequently antedate the acute infarction.[17] These differences, however, do not detract from the appropriateness of the animal model for study of the basic electrophysiologic disturbances after acute ischemic injury of the His-Purkinje system. Localization of the conduction disturbance in the proximal His-Purkinje system in our experiment is consistent with the anatomic distribution of the anterior septal artery in dogs. Ligation of the latter usually produces ischemia in the area of the muscular interventricular septum containing the distal portion of the A–V node, bundle of His and major portions of the right and left bundle branches.[18,19]

Demonstration of the transient nature of acute ischemic conduction disturbances in the canine proximal His-Purkinje system confirms the clinical experience of the temporary nature of many instances of A–V conduction disturbances and bundle branch block complicating acute myocardial infarction.[20,21] These observations are consistent with pathologic data in dogs[22] and man[23,24] suggesting relative immunity of the conducting tissue to ischemia at least in a morphologic sense. The relative sparing of the conduction fibers suggests that factors other than hypoxia itself may be responsible for the transient conduction disturbance.[24–27] These factors, released by the injured myocardial cells and other inflammatory cells, may accumulate and alter the ionic environment surrounding the conduction tissue and hence its electrophysiologic properties. They may be dissipated or washed out later on with the development of effective collateral circulation resulting in reversal of the conduction disturbance. The observation that collateral flow may not be sufficiently great to reverse the ischemic electrocardiographic changes probably reflects metabolic differences between contractile and conducting fibers.[24] An important factor implicated in acute ischemic rhythm disorders is the leak of large amounts of potassium ion from the intracellular to the extracellular space.[27]

Electrophysiologic Correlation

Correlation with in vitro studies: Our in vitro studies, revealing characteristic changes of the Purkinje fibers in the proximal His-Purkinje system involved in the acute ischemic process, are relevant to in vivo observations. Purkinje fibers in the proximal segment of the bundle branch system usually showed marked change in their action potentials. Partially depolarized fibers with a low resting potential, slowly rising phase zero and a diminished action potential amplitude were frequently seen (Fig. 12A). The electrical excitability and refractoriness of these fibers differed markedly from the properties of normal Purkinje fibers, and the duration of complete recovery of excitability was greater than that of the action potential. These fibers usually display a poor response to stimuli applied late in diastole after completion of the action potential (Fig. 12B). The fibers showed primarily a time-dependent rather than a voltage-dependent response to cycle length changes. This response is somewhat similar to the normal response of some cells in the sinoatrial and atrioventricular nodes.[28] Most of the electrophysiologic characteristics of these fibers can be explained by an increase in the extracellular potassium ion concentration in the ischemic zone. Previous studies of Purkinje fibers superfused with a high concentration of potassium ion revealed reduction in the resting potential, slowing of the upstroke velocity, decrease of the electrotonic spread and elevation of the threshold potential.[29,30] All of these factors can contribute to the reduction of conduction velocity.[30,31] Our observations suggest that the initial phase of tachycardia-

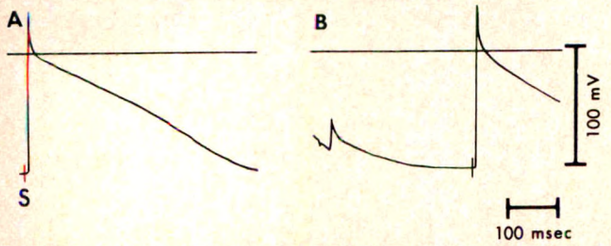

FIGURE 13. A, transmembrane potential recorded from a Purkinje fiber in the proximal portion of a canine right bundle branch 24 hours after ligation of the anterior septal artery. Note the prolonged action potential with characteristic changes of the voltage time course of the membrane potential during repolarization. **B,** stimulation at a cycle length of 300 msec showing 2:1 response. Note the very low action potential generated by stimulation during the terminal part of phase 3.

dependent block in the proximal His-Purkinje system is dependent on the characteristic response of the partially depolarized Purkinje fibers to shortening of the cardiac cycle.

We have demonstrated Purkinje fibers with prolonged action potentials in specimens obtained 24 hours after ligation. These fibers show a very characteristic change of the voltage time course of the membrane potentials during repolarization with shortening of phase 2, the early portion of phase 3 and a protracted terminal part of phase 3. These changes are particularly clear in cells showing full amplitude of resting and action potentials (Fig. 13A). In association with the altered action potential, these cells show evidence of reduced membrane responsiveness. Similar Purkinje fiber properties have been demonstrated in our laboratory[32] and by others[33] in the infarcted zone after ligation of the anterior descending artery, and we have shown that the action potential duration usually returns to normal within 3 to 4 days. These cells usually demonstrate a 2:1 response to shortening of the cycle length which can be explained by stimulation during the terminal part of phase 3, which results in a small action potential with a shortened duration so that the next stimulus usually falls outside phase 3 and thus conducts normally (Fig. 13B). The characteristic electrophysiologic response of these cells represents a voltage-dependent phenomenon and cannot explain the development of a 1:1 tachycardia-dependent bundle branch block. By contrast, partially depolarized Purkinje fibers may show an alternation of the action potential configuration at a certain degree of shortening of the cardiac cycle (Fig. 12B).In this case, however, a significant conduction delay is present in every cycle to give rise to a 1:1 pattern of complete bundle branch block. Thus, a time-dependent response of partially depolarized Purkinje fibers is probably the main electrophysiologic mechanism for tachycardia-dependent

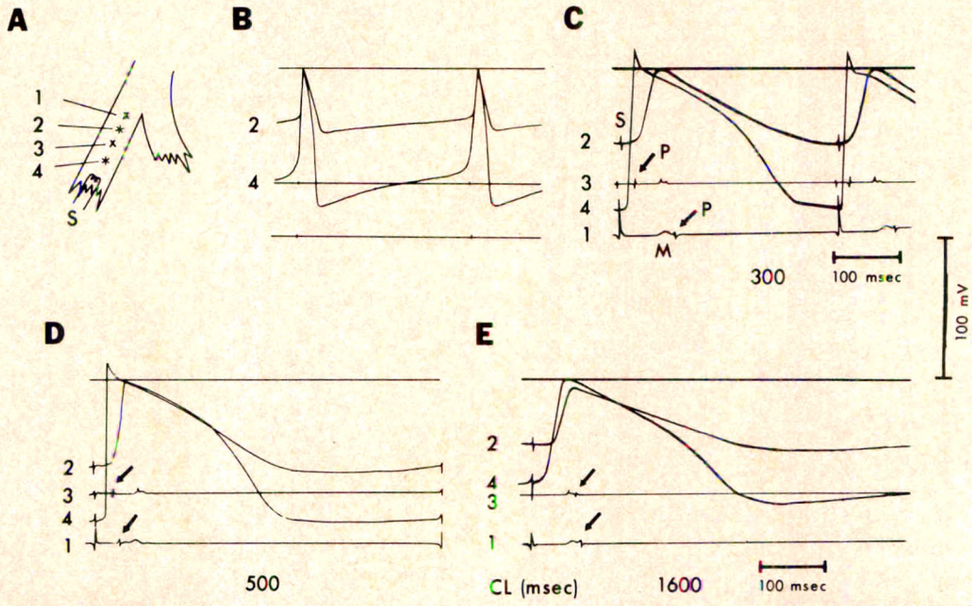

FIGURE 14. Records of the transmembrane potential of two Purkinje fibers from a proximal and a more distal portion of the left bundle branch system (2 and 4) and two electrograms (1 and 3). The specimen was obtained 5 hours after ligation of the anterior septal artery. Panel **A** shows the arrangement of the stimulating (S) and recording electrodes. Panel **B** shows spontaneous firing at a rate of 40/min. Note that the proximal fiber has a low resting potential and a slow rising action potential of small amplitude. The distal fiber shows slight reduction of resting potential and a "normal" slope of phase-4 depolarization. Panels **C to E** show the response of the two fibers to rapid (CL [cycle length] 300 msec), intermediate (CL 500 msec) and slow (CL 1,600 msec) driving frequencies. Note reduction of amplitude and upstroke velocity of action potential of the distal fiber at the slow driving rate. The transmembrane (M) potential of the proximal fibers shows lesser changes at different cycle lengths. Note that the downstream electrogram (1) shows delay of the Purkinje spike (P, marked by arrow) both at the rapid and slow driving frequencies as compared to the intermediate rate. Delay of the Purkinje spike will be reflected in the surface electrogram by the inscription of a bundle branch block pattern.

conduction disorders in the proximal His-Purkinje system under these experimental conditions.

Bradycardia-dependent block, phase 4 depolarization and extracellular potassium ion concentration: The concomitant demonstration of bradycardia-dependent block is particularly interesting since increased extracellular potassium ion is known to depress phase-4 depolarization. Two of our in vivo observations are particularly pertinent. The finding that long bradycardic intervals are usually necessary to illustrate bradycardia-dependent block suggests a normal or slowly rising rather than "enhanced" slope of phase-4 depolarization. On the other hand, the observation of long bradycardic intervals without pacemaker escape may point to a shift of the threshold potential toward zero. We have found that, when studied progressively distally along the bundle branch system, the Purkinje fibers show a lesser decrease of the resting potential and a normal or near normal slope of phase-4 depolarization (Fig. 14B). These cells can show a bradycardia-dependent conduction disturbance at slow driving frequencies, and the shift of the threshold potential rather than enhanced phase-4 depolarization may be the crucial factor in the display of bradycardia-dependent block. Such a shift in threshold potential permits gradual reduction of the membrane potential to levels at which significant decrement of conduction is likely to occur. This effect will be accentuated if there is an initial slight to moderate reduction in the resting potential of the kind expected to occur as a result of depolarization induced by a moderate increase in extracellular potassium ion. Another factor that can contribute to bradycardia-dependent block without marked enhancement of phase-4 depolarization is decrease of the membrane responsiveness.[34] Thus, bradycardia-dependent bundle branch block can be explained by the characteristic electrophysiologic alterations of Purkinje fibers at the periphery of the ischemic zone (distally located in the bundle branch system in our preparation) where the increase in extracellular potassium ion concentration is not as great as in the more ischemic proximally located zone. Figure 14, C to E, shows the characteristic response of two Purkinje fibers from a proximal and a more distal portion of the bundle branch system to rapid, intermediate and slow driving frequencies.

Concomitant tachycardia- and bradycardia-dependent block: In a recent series of papers, Rosenbaum's group[35–37] addressed themselves to the observation of concomitant tachycardia- and bradycardia-dependent bundle branch block. They hypothesized that tachycardia-dependent block can be explained by prolonged action potential duration of Purkinje fibers (phase-3 block), whereas bradycardia-dependent block is related to hypopolarization plus spontaneous diastolic depolarization (phase-4 block). Our in vivo and in vitro observations do not wholly support these recently published hypotheses. Tachycardia-dependent block in the proximal His-Purkinje system after acute myocardial ischemia was found to be related to a time-dependent rather than voltage-dependent response of partially depolarized Purkinje fibers. Hoffman[38] recently pointed to the difficulty of interpretation of tachycardia-dependent block based on marked prolongation of the action potential duration when durations of up to 1.8 seconds[37] sometimes have to be postulated. Although he indicated the possible role of prolonged action potentials recorded from Purkinje fibers 24 to 72 hours after occlusion, we[32] have demonstrated that this prolongation is limited both in value (a maximum of 750 msec) and duration (1 to 4 days after infarction). More significantly, we observed that these cells usually showed a 2:1 response to shortening of the cycle length which would not explain tachycardia-dependent bundle branch block.

Enhanced phase-4 depolarization and bradycardia-dependent block: Our observations suggest that the previously reported relation between enhanced phase-4 depolarization of the pacemaker cells and bradycardia-dependent conduction disturbances[5] is not applicable to our experimental findings. We found an absence of a relation between enhanced automaticity and bradycardia-dependent conduction disturbances, which is primarily related to the difference in behavior of the threshold potential. This was based on the following two observations: (1) In the early stage after acute ischemic injury when there was no enhanced automaticity, bradycardia-dependent block was usually demonstrated; (2) several hours after ligation of the anterior septal artery when enhanced automaticity began to be observed it was usually possible to illustrate that bradycardia-dependent block did not occur at rates significantly slower than the escape rate. Moreover, the escape rhythm did not necessarily arise from the site of maximal conduction disturbance in the bundle branch system. In relation to this point, we have demonstrated that in the presence of bradycardia-dependent conduction disturbance, escape rhythms arising from the A–V node, bundle of His, proximal portion of the diseased bundle or from the other bundle branch system may have exactly the same QRS configuration in conventional leads (Fig. 6). This clearly illustrates the limitation of attempting to localize the site of origin of escape rhythm from the conventional electrocardiogram.[39]

The electrophysiologic mechanisms underlying tachycardia- and bradycardia-dependent block in the proximal His-Purkinje system after acute myocardial ischemia may prove to be more complicated than those we have outlined. The possibility exists that in different clinical settings other mechanisms may be operating. Greater insight into the mechanisms of conduction disorders in the His-Purkinje system will probably have to await further electrophysiologic studies.

Acknowledgment

We acknowledge the technical assistance of Messrs. Jorge Rodriguez, Edward J. Berbari, Israel Dingle and David Young, Jr., and the secretarial assistance of Ms. Marie Ellis.

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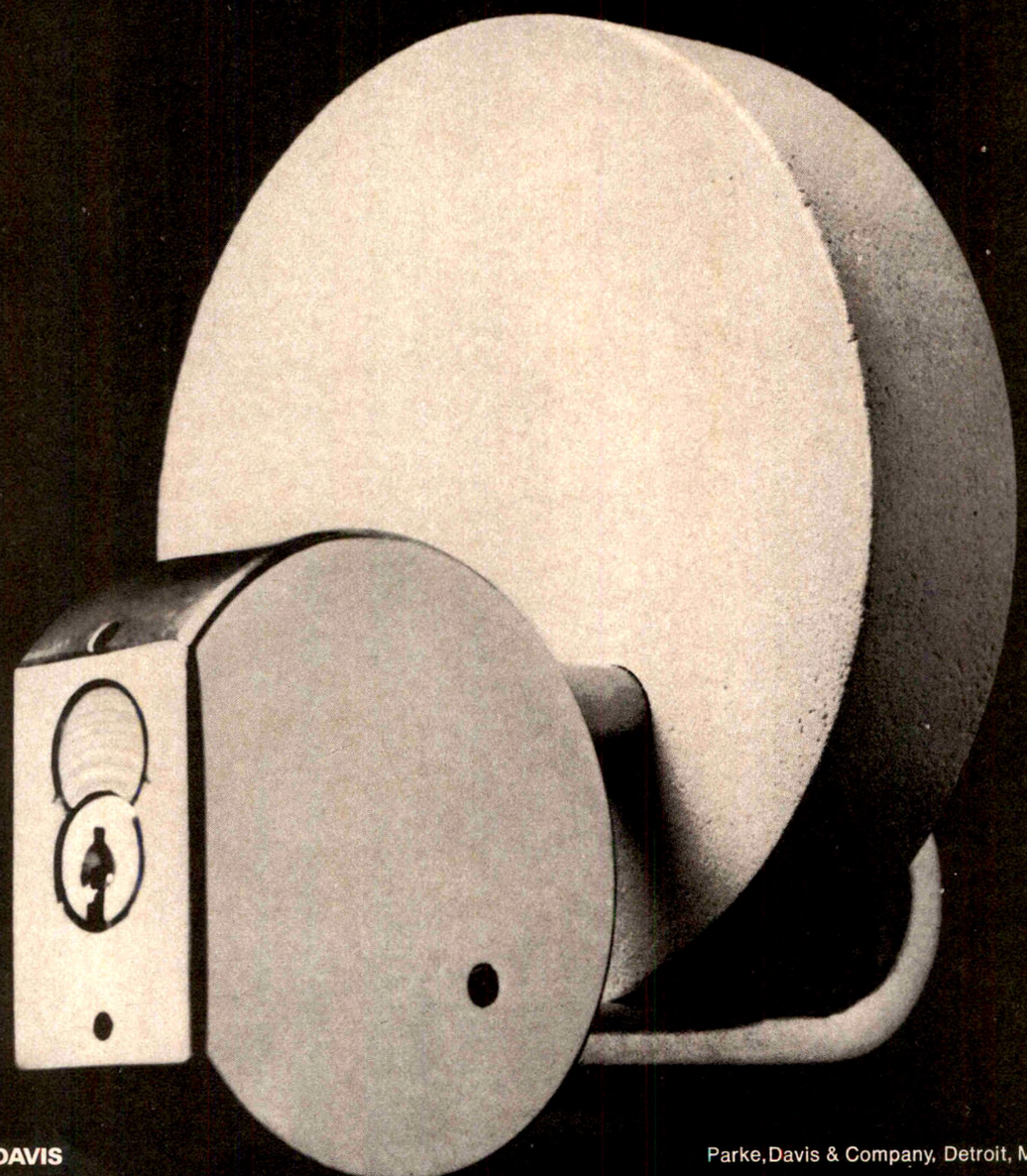

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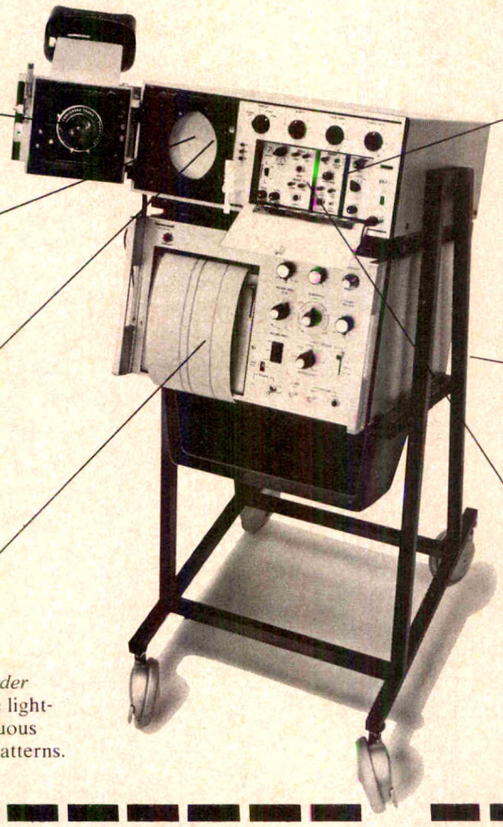
Two new modules give the Smith Kline Instruments Ekoline 20A® an unmatched multi-trace capability. The Isolated Sweep/EKG Module and the Multi-Parameter Amplifier Module enable the E20A Ultrasonoscope to produce traces for ultrasound, EKG, phono and carotid pulse or apex. Combine this with the Fiber-optic Recorder and the result is high quality, grey scale strip chart recordings of pertinent information—at a surprisingly low cost.

1. *New Oscilloscope Camera* features built-in electronic shutter release, uses high-speed 'Polaroid' film.

2. *New High-Resolution Oscilloscope* is standard on all 'Ekoline 20A' instruments, gives outstanding display of all echo patterns.

3. *New Long-Persistence Oscilloscope,* available as optional equipment, uses P7 phosphor to provide best possible display of M-mode echo patterns.

4. *New Fiber-Optic Line-Scan Recorder* utilizes fiber-optic CRT to expose light-sensitive paper, producing continuous "strip-chart" recordings of echo patterns.



5. *New Isolated Sweep/EKG System* Converts A-Mode echo display from a moving organ into M-Mode display. Features isolated, linear, and movable EKG.

6. *New Equipment Cart* conveniently houses 'Ekoline 20A' and Recorder. Permits complete system to be readily moved to any location throughout the hospital.

7. *New Multi-Parameter Amplifier Module* provides the capability for echo, EKG, phono and carotid pulse or apex traces.

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☐ Send detailed literature.

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440 Page Mill Road
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Telephone: (415) 321-9200

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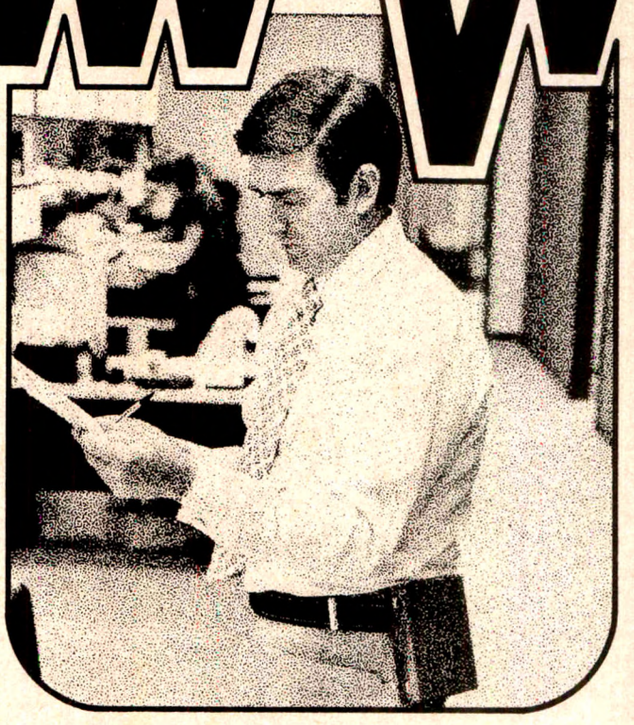

Model 5000 Dyna-Gram® Recorder

The Model 5000 Dyna-Gram® Recorder for Holter Electrocardiography.

The Model 5000 is a new 24-hour cassette recorder with electronic timing and a digital patient clock for precise correlation of the ECG with patient activities and symptoms. The advanced design of the Model 5000 includes an exclusive circuit to minimize electrode artifact. The rechargeable Dyna-Gram® Power-Pack provides continuous 24-hour recording capability *without* turning the cassette. Compact and light weight, the Model 5000 Dyna-Gram® Recorder can be worn with a waist belt or a shoulder strap.

No purchase of costly processing equipment is required. Your recorded Dyna-Gram® cassettes will receive Cardio-Dynamics comprehensive analysis using the unique Dyna-Gram® III Analyzer System.

A quality line of cassettes, disposable electrodes, and related patient hookup supplies is available.

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Setting Standards in Holter Electrocardiography

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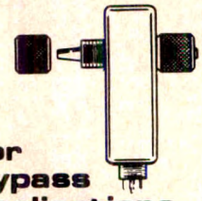
FLOW PROBES



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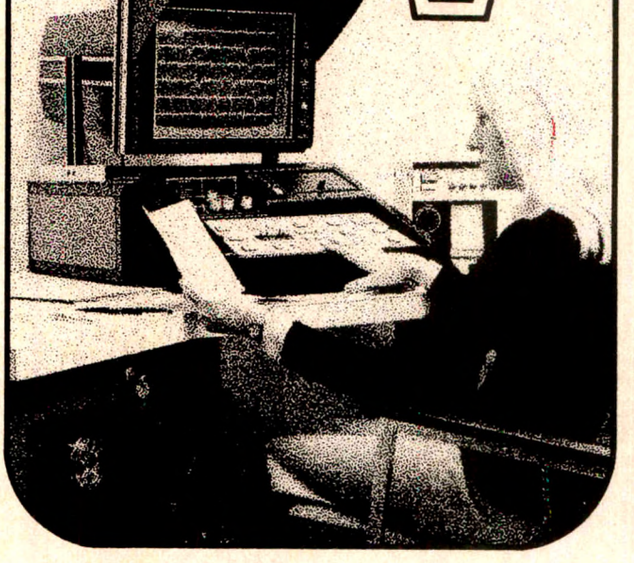

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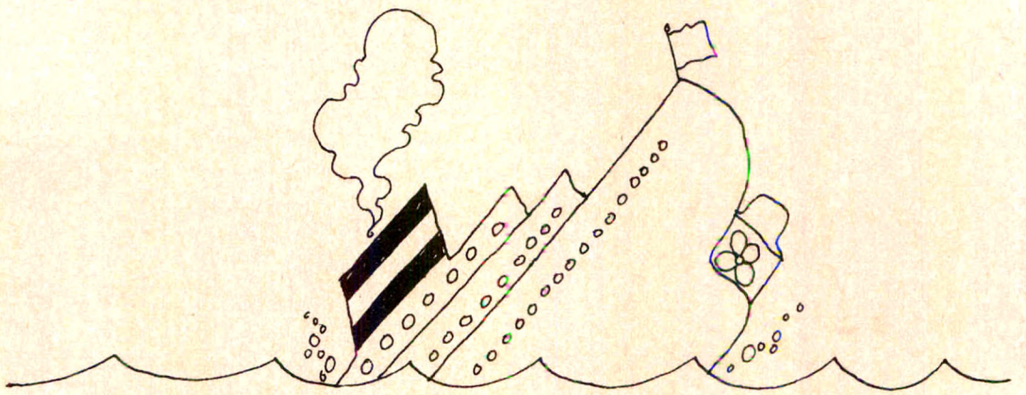
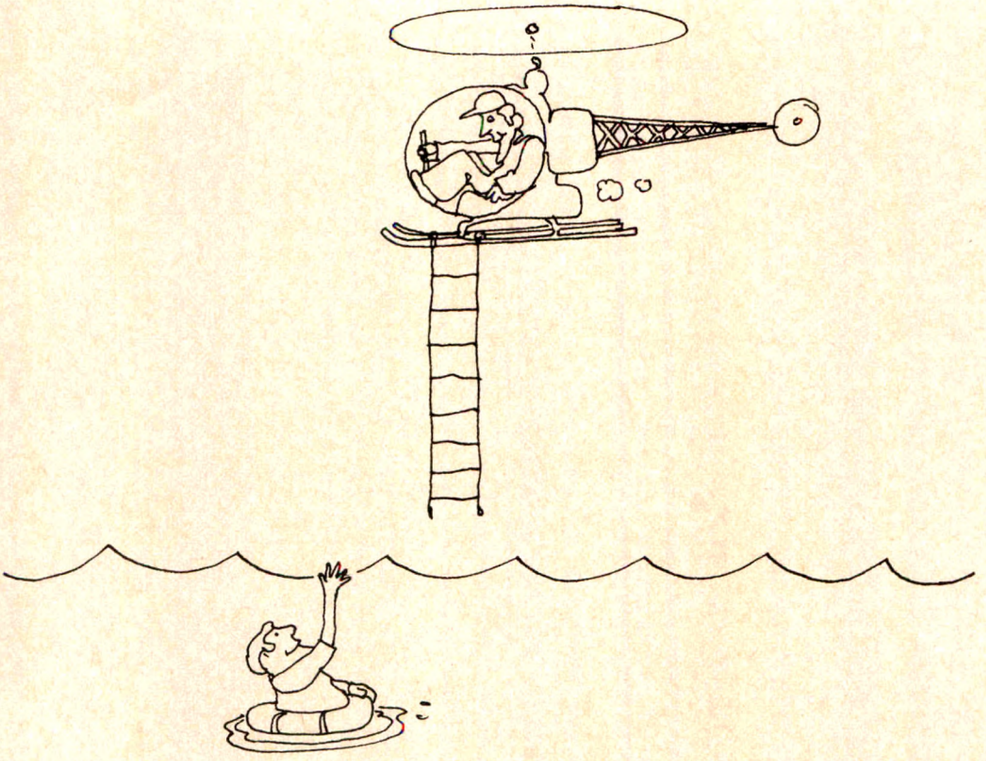


The cure:



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The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

Persantine — over a decade of use

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Persantine — give enough — long enough

The recommended dosage: 50 mg. t.i.d. at least one hour before meals. *Give enough, long enough* — several weeks or longer of continuous therapy may be needed to see response.

Persantine® Tablets of 25 mg.
dipyridamole

the non-nitrate
coronary vasodilator

*INDICATIONS – Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS – No specific contraindications are known.

PRECAUTIONS – Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS – Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION – The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

Medieval Engraving
Engraving of a heart and the child Jesus, surrounded by cherubs. The transcription states, "Whoever holds Him in his heart is assured of eternal joy."

The engraving was made by "E.S." in 1467. It is in a collection of engravings in Berlin.

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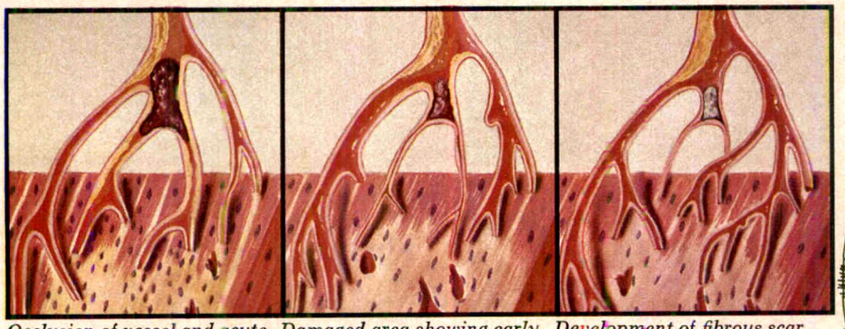
As the infarct heals,



Occlusion of vessel and acute infarct of the myocardium.

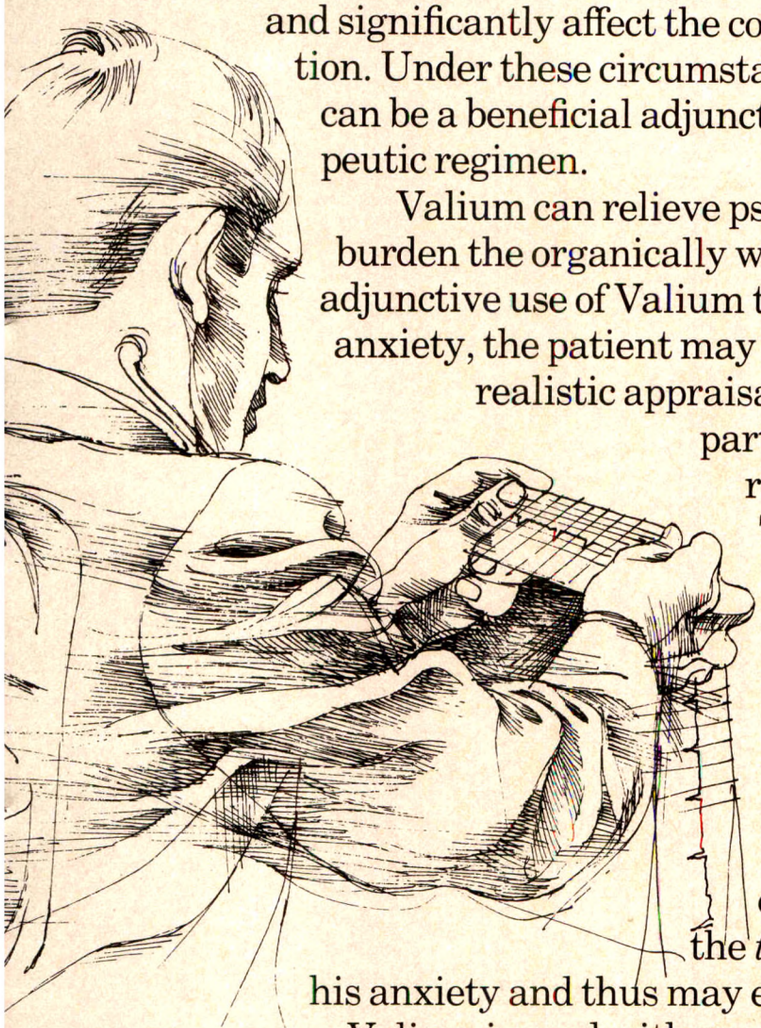
Damaged area showing early collateral vessel formation.

Development of fibrous scar and healing of infarcted area.

will psychic tension affect the patient's rehabilitation?

ROCHE

After the MI patient's acute episode has been successfully managed, a program of rehabilitation is begun. At times the overly tense cardiac patient may present a special problem. Although you continue to encourage a positive outlook through counseling and enlistment of support from the patient's family, psychic tension may remain, and significantly affect the course of rehabilitation. Under these circumstances, Valium (diazepam) can be a beneficial adjunct to the patient's therapeutic regimen.



Valium can relieve psychic tension that may burden the organically weak heart. As a result of adjunctive use of Valium to relieve unwarranted anxiety, the patient may be able to arrive at a more realistic appraisal of his situation and participate more fully with his rehabilitation program.

Therapy should normally be continued until the patient's anxiety has been reduced to tolerable levels.

Since the cardiac patient may be particularly prone to tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *t.i.d.* schedule can relieve his anxiety and thus may encourage sleep.

Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticholinergics and antacids. The most commonly reported side effects have been drowsiness, fatigue and ataxia. Patients taking Valium should be cautioned against driving or operating dangerous machinery.

Valium®(diazepam)
2-mg, 5-mg, 10-mg tablets

when you consider it essential to keep the heart patient calm

Please turn page for a summary of product information.

When you consider it essential to keep the heart patient calm

- Valium (diazepam) can relieve psychic tension and anxiety that may burden the organically weak heart and interfere with the patient's course of rehabilitation.
- Valium works promptly in most patients. Significant improvement is usually noted during the first few days of therapy, although some patients may require more time to respond.
- Adjustments in dosage can alter clinical response. With appropriate titration, a regimen can be tailored to the patient's individual needs.
- Valium has a wide margin of safety in the usual oral dosage range and generally does not significantly affect respiration or pulse.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 1000.

ROCHE

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Division of Hoffmann-La Roche Inc.
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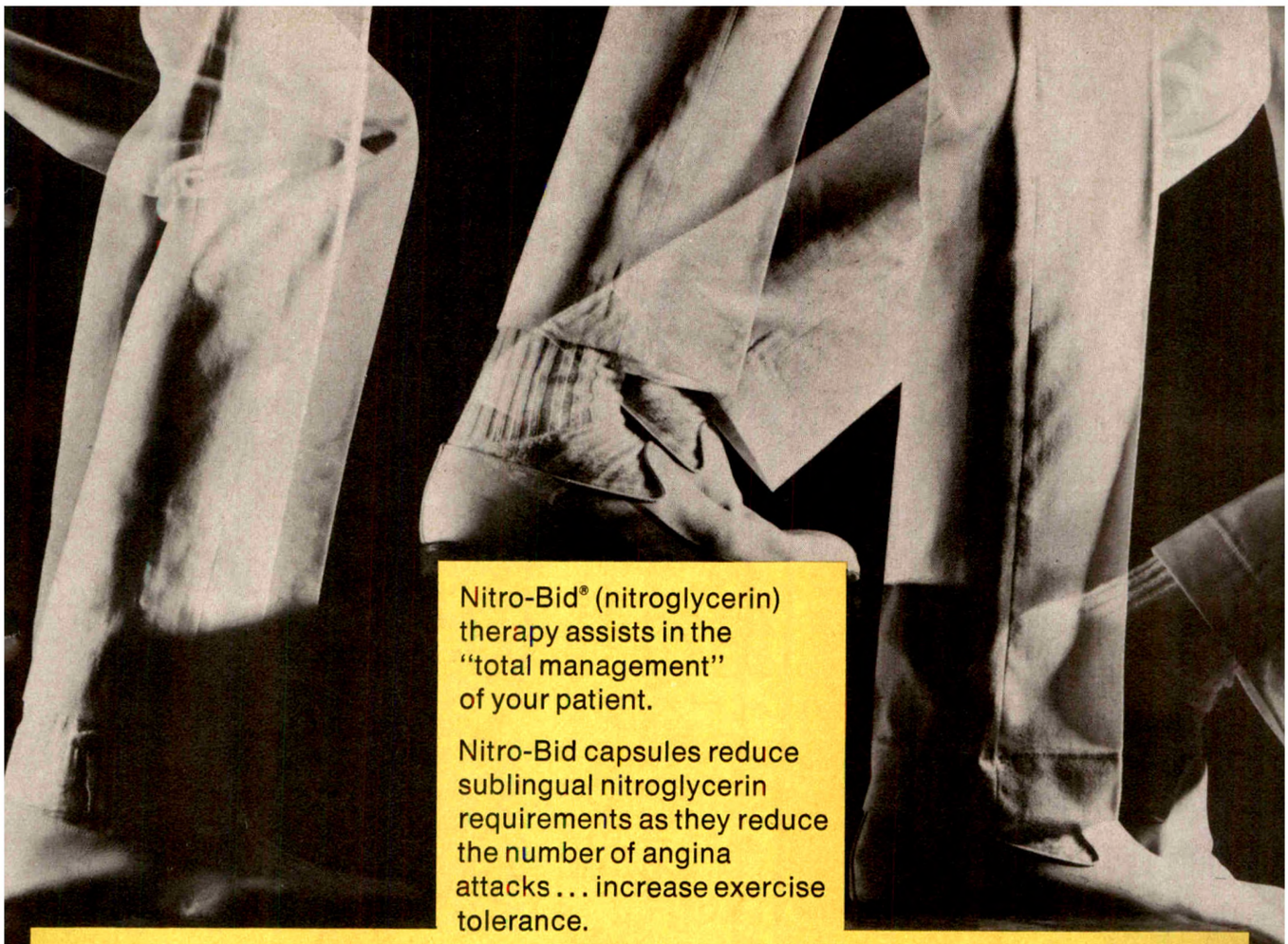

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After the classic "2-Step" Test aids in a diagnosis of angina, sustained-release Nitro-Bid® (nitroglycerin) is a logical third step. Here's why.

In angina secondary to arteriosclerotic heart disease, sustained-release Nitro-Bid® (nitroglycerin) therapy assists in the "total management" of your patient.

Nitro-Bid capsules reduce sublingual nitroglycerin requirements as they reduce the number of angina attacks . . . increase exercise tolerance.

Sustained-release Nitro-Bid Plateau CAPS® provide a metered sequence of medication during the night to protect against nocturnal angina attack.

In titrating dosage, availability of different strengths "...is quite an asset..."[1]

Nitro-Bid 2.5 and Nitro-Bid 6.5 capsules afford two dosage strengths for convenience in increasing or decreasing dose to accommodate patient symptoms.

NITRO-BID® 2.5
(nitroglycerin 2.5 mg) Plateau CAPS®

NITRO-BID® 6.5
(nitroglycerin 6.5 mg) Plateau CAPS®

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

*"Possibly" effective:
For the management, prophylaxis or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12 hour intervals.
Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

Another patient benefit product from PHARMACEUTICAL DIVISION MARION LABORATORIES, INC. KANSAS CITY MISSOURI 64137

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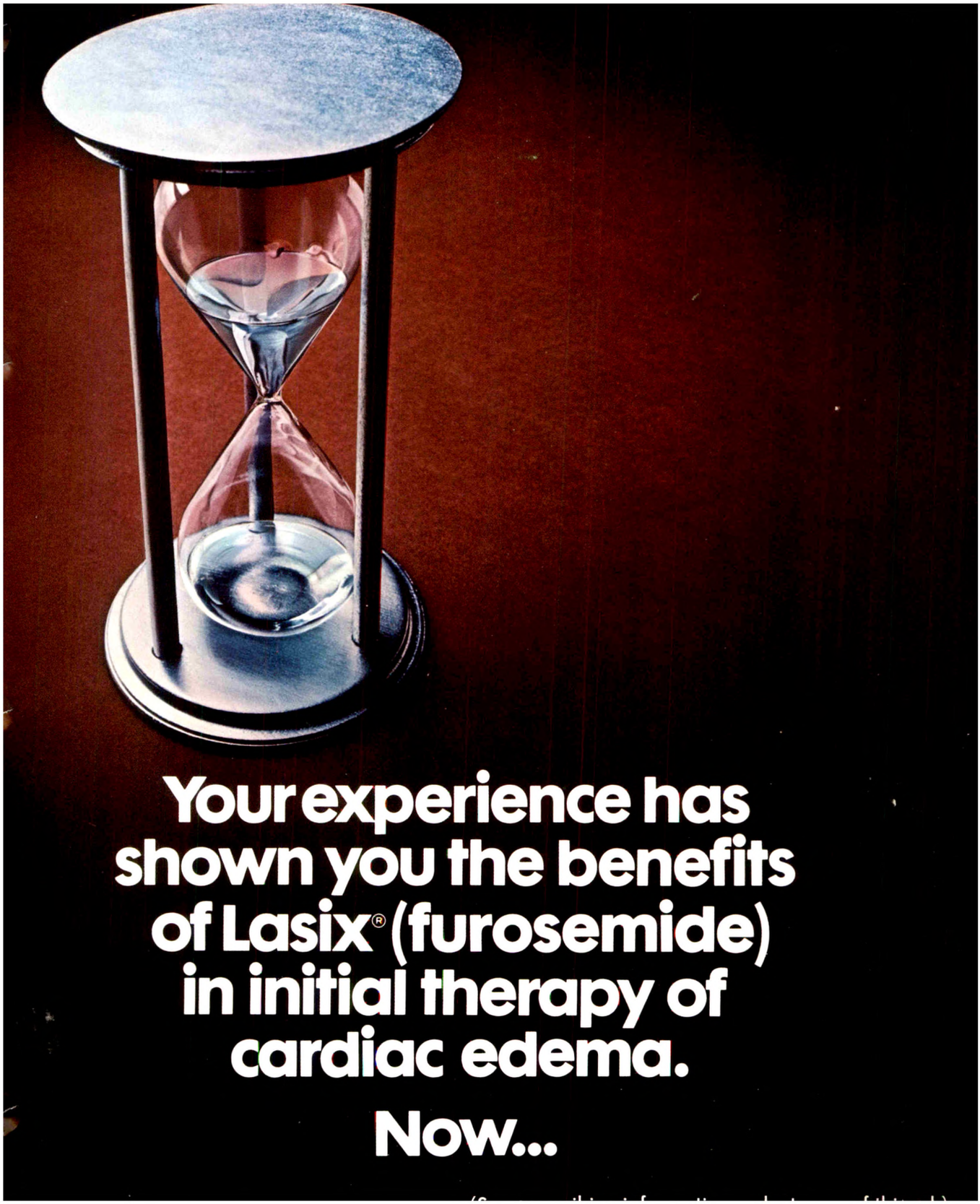
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of Lasix® (furosemide)
in initial therapy of
cardiac edema.
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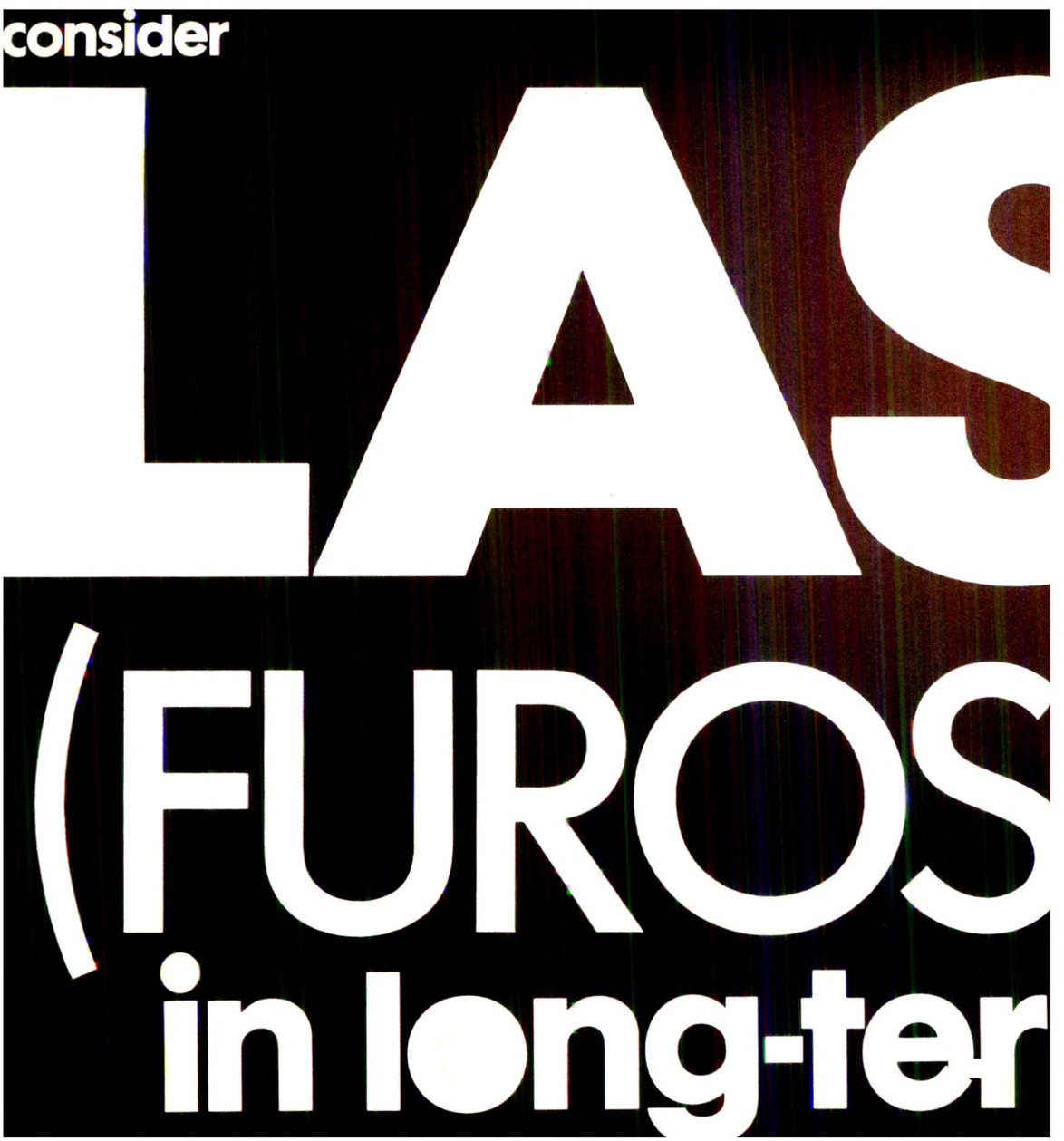
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wide range of effectiveness allows you to treat most degrees of cardiac edema.

dry weight can be reliably and safely maintained by adjusting the dose to fit your patient's needs. With doses exceeding 80 mg /day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

patient inconvenience is minimal since diuresis is usually complete within six to eight hours.

(See Lasix® [furosemide] prescribing information on last page of this

LASIX® (FUROSEMIDE)

TABLETS 40 mg

in long-term therapy

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "DOSAGE AND ADMINISTRATION".)

DESCRIPTION—Lasix is a diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by:

- a high degree of efficacy;
- a rapid onset of action;
- a comparatively short duration of action;
- a ratio of minimum to maximum effective dose higher than 1:10;
- the fact that it acts not only at the proximal and distal tubules but also at the ascending limb of Henle's loop.

Lasix is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

INDICATIONS—Lasix is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

Hypertension—Lasix may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of child-bearing potential. (See "ADDITIONAL INFORMATION".)

Lasix is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix is contraindicated in patients with a history of hypersensitivity to this compound.

Until more experience is accumulated in the pediatric use of Lasix, children should not be treated with the drug.

WARNINGS—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix.

PRECAUTIONS—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix is administered, since Lasix potentiates the hypotensive effect of antihypertensive medications.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix precedes its oral use, it should be kept in mind that cases of reversible deafness and tinnitus following the injection of Lasix (furosemide) have been reported. These adverse reactions occurred when Lasix was injected at doses exceeding several times the usual therapeutic dose of 20 to 40 mg.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour post-prandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

It has been reported in the literature that diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix, and it is advisable to discontinue Lasix for one week prior to any elective surgery.

ADVERSE REACTIONS—Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura) may occur. Rare cases of agranulocytosis have occurred which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli (see "WARNINGS"), and acute pancreatitis.

Lasix-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

As far as hyperglycemia is concerned, see "PRECAUTIONS".

DOSAGE AND ADMINISTRATION—The usual dose of Lasix is 40 to 80 mg given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced.

If the diuretic response with a single dose of 40 to 80 mg is not satisfactory; e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). The dose of Lasix may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states. Higher doses are currently under investigation.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents; e.g., reserpine, rather than to increase the dose of Lasix.

Until more experience is accumulated in the pediatric use of Lasix, children should not be treated with the drug.

HOW SUPPLIED—Lasix (furosemide) Tablets are supplied as white, monogrammed, scored tablets of 40 mg in amber bottles of 100 (6505-00-062-3336), 500 (6505-00-254-5546A), and Unit Dose 100's (20 strips of 5) 6505-00-117-5982).

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

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Blood Flow Velocity Measured at the Mitral Valve of Man

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Phasic mitral valve blood flow velocity was measured in 30 conscious persons with the Doppler ultrasonic flowmeter catheter. Mitral valve flow velocity is chracterized by a a large pandiastolic wave followed by a smaller systolic component. Deep inspiration resulted in a decline of peak mitral valve flow velocity; expiration had an opposite effect. The Valsalva maneuver produced a marked decline of peak flow velocity, which lasted for the duration of straining. Atrial and ventricular extrasystoles caused a diminution of peak mitral valve flow velocity, generally related to the duration of the extrasystolic coupling intervals. Brief episodes of ventricular tachycardia effected a decline of peak mitral valve flow velocity and the wave forms became completely irregular. These findings represent the first detailed description of phasic instantaneous mitral valve flow velocity in conscious man in a variety of physiologic and abnormal states.

Phasic blood velocity and volumetric blood flow have been measured at the mitral valve of experimental animals by means of surgically introduced electromagnetic flowmeters[1,2] and pressure differential techniques.[3] In these latter studies, estimation of mitral valve flow required general anesthesia, thoracotomy and incorporation of flowmeters into mitral valve prostheses[1] or the left atrial myocardium,[2] or direct insertion of pressure diffferential needles near the mitral valve ring.[3] We describe here instantaneous measurement of phasic mitral valve blood flow velocity in conscious man utilizing the Doppler flowmeter catheter technique.

Material and Methods

Thirty subjects comprised the study group. There were 22 men and 8 women whose ages ranged from 18 to 66 years (mean 49). Five patients had normal cardiac findings and 25 had heart disease. In this latter group 14 patients had coronary artery disease, and 11 had other forms of acquired or congenital heart disease. All diagnoses were made on the basis of complete right and left heart catheterization, selective coronary cineangiography and indicator-dilution curves. Normal subjects were studied because of the presence of chest pain or systolic murmurs originally thought to represent organic heart disease.

Mitral valve blood flow velocity was measured with a catheter tip[4] adaptation of Franklin's Doppler ultrasonic flowmeter.[5] This device has been utilized in our laboratory for the study of right atrial,[6] right ventricular,[7] aortic,[8] coronary arterial,[9] carotid arterial,[10] renal arterial[11] and superior mesenteric arterial[12] blood flow velocity patterns in man. The application of the Doppler flowmeter for the measurement of blood velocity in the left ventricle of man has recently been described.[13] With use of 1 percent lidocaine for local anesthesia, the right or left brachial artery and a medial antecubital vein were isolated. The flowmeter-tipped catheter was introduced into the artery and passed in retrograde fashion under fluoroscopic observation to the ascending aorta. The catheter was then advanced across the aortic valve into the left ventricle and positioned at the mitral valve (Fig. 1). Signals arising from mitral valve blood flow were identified by a predominant diastolic wave that was apparent on the oscilloscope display and will be described under Results.

From the Institute for Cardiovascular Diseases, Good Samaritan Hospital, Phoenix, Ariz. This study was supported in part by the Nichols' Memorial Fund, Phoenix, Ariz. Manuscript accepted July 25, 1973.

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The large diastolic component was evident during audible monitoring of the Doppler frequency shift. A saline-filled no. 7 or 8 bipolar Zucker catheter connected to a Statham P 23Db strain gauge was introduced into the vein for the purpose of obtaining right atrial, right ventricular or pulmonary arterial pressures. Flow velocity signals, right heart pressures, lead II of the electrocardiogram and at times external carotid arterial pulse tracings were simultaneously recorded on an Electronics for Medicine DR-12 oscilloscopic photographic recorder operated at various paper speeds. The flow velocity audio signals, voltage signals and other physiologic data were recorded on an eight channel Sanborn magnetic tape recorder.

Results

Blood flow velocity at the mitral valve during sinus rhythm: Blood flow velocity at the mitral valve was phasic, continuous and characterized by a large pandiastolic wave followed by a smaller and shorter peaked systolic component. The ascending limb of the diastolic wave was recorded rapidly, immediately after inscription of the dicrotic notch and second heart sound on the simultaneously recorded external carotid pulse tracing and phonocardiogram, respectively. The smaller systolic wave had a rapid upstroke and an early midsystolic downstroke. Peak systolic flow velocities usually attained levels which were 25 to 75 percent of the values for peak diastolic flow velocities and were recorded during the midsystolic *x* descent of simultaneous right atrial pressure recordings (Fig. 2). Signals obtained from other left ventricular cavity sites were characterized by larger systolic waves.[13] Differences between recordings obtained from the mitral valve area and other left ventricular sites were appreciated during careful withdrawal and advancement of the catheter tip under fluoroscopic control (Fig. 3). In 50 percent of cases, left atrial contraction resulted in a small presystolic flow velocity wave that peaked after the right atrial pressure *a* wave and a fourth heart sound on a simultaneously recorded phonocardiogram. This presystol-

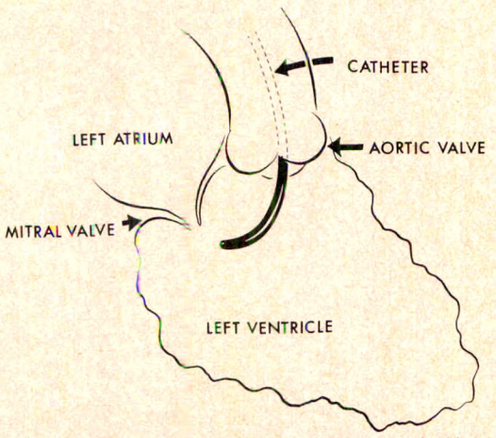


FIGURE 1. Schematic diagram demonstrating the position of the Doppler flowmeter catheter during measurement of mitral valve blood flow velocity.

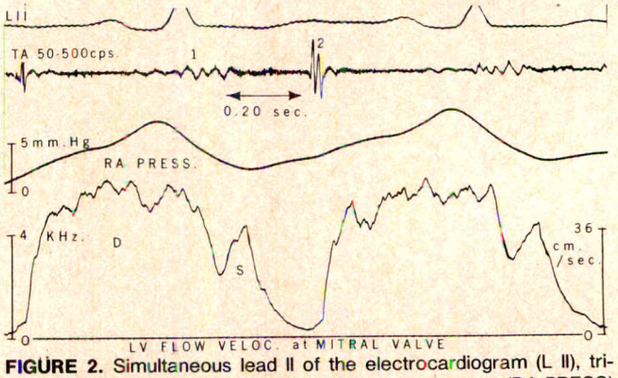


FIGURE 2. Simultaneous lead II of the electrocardiogram (L II), tricuspid area phonocardiogram (TA), right atrial pressure (RA PRESS) and mitral valve blood flow velocity recorded in a normal 65 year old woman. Note the rapid inscription of diastolic (D) flow velocity during concurrent recording of the second heart sound (2). The smaller systolic (S) wave occurs at the time of inscription of the first heart sound (1) and peaks during midsystole when the simultaneously recorded right atrial pressure is at its lowest level.

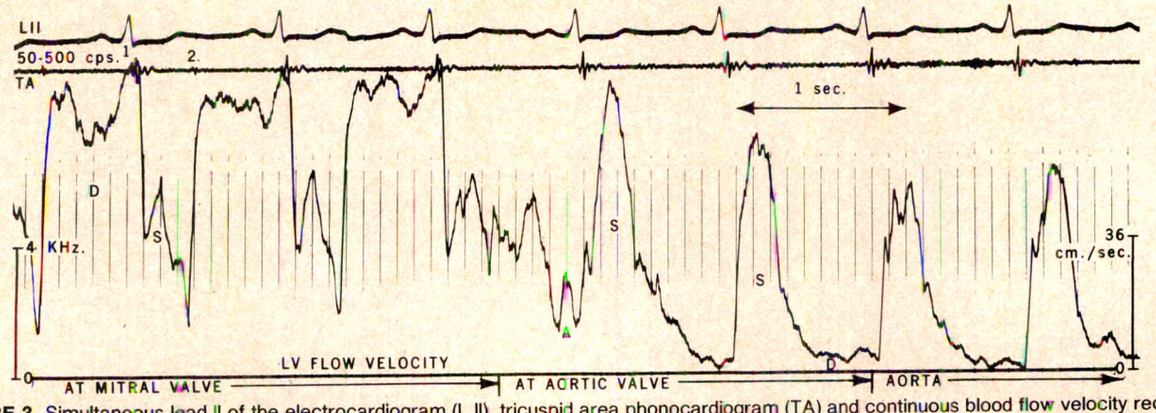
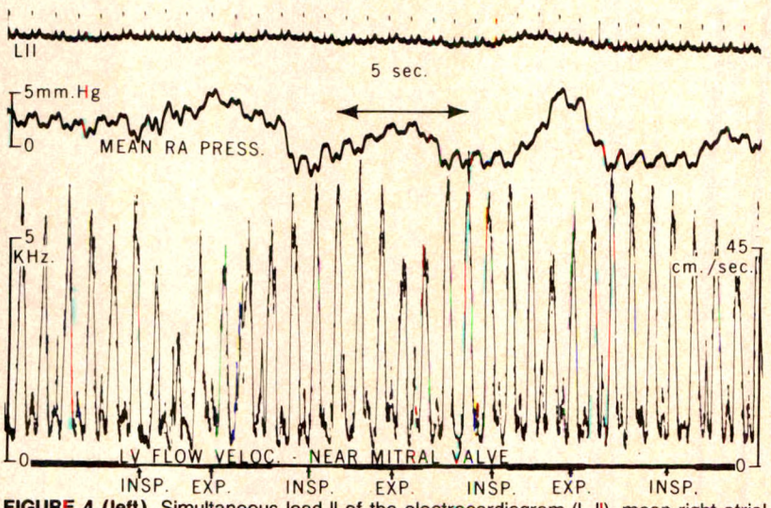


FIGURE 3. Simultaneous lead II of the electrocardiogram (L II), tricuspid area phonocardiogram (TA) and continuous blood flow velocity recorded during withdrawal of the Doppler catheter flowmeter tip from the mitral valve position toward the aortic valve in a 54 year old man with coronary artery disease. Note the decrease of diastolic flow velocity (D) and increase of systolic flow velocity (S) as the catheter tip is maneuvered to the left ventricular outflow tract and withdrawn across the aortic valve. LV = left ventricular; 1 = first heart sound; 2 = second heart sound.

ic wave did not increase peak diastolic flow velocity at the mitral valve by more than 15 percent.

Effects of respiration and Valsalva maneuver: During deep inspiration and expiration, there were cyclic alterations of peak diastolic flow velocity at the mitral valve. Inspiration was associated with a decline of peak mitral valve blood flow velocity; lowest values for peak flow velocity usually corresponded to an increase of simultaneously recorded mean right atrial pressure. Expiration had exactly the opposite effects—an increase of peak diastolic flow velocity with concomitant decline of mean right atrial pressure (Fig. 4). The Valsalva maneuver resulted in a marked reduction of peak mitral valve blood flow velocity, which lasted as long as the straining continued (Fig. 5).

Effects of arrhythmias: Atrial premature beats resulted in reductions of peak flow velocity at the mitral valve that were generally dependent on the preceding extrasystolic coupling interval; the shorter the coupling interval, the greater was the diminution of peak flow velocity. In a single subject with atrial bigeminy, reductions of peak systolic and diastolic mitral valve blood flow velocity were always associated with the atrial extrasystoles, resulting in persistent alternation of recorded wave forms (Fig. 6). Similarly, ventricular extrasystoles produced a decrease of peak mitral valve blood flow velocity, with greater



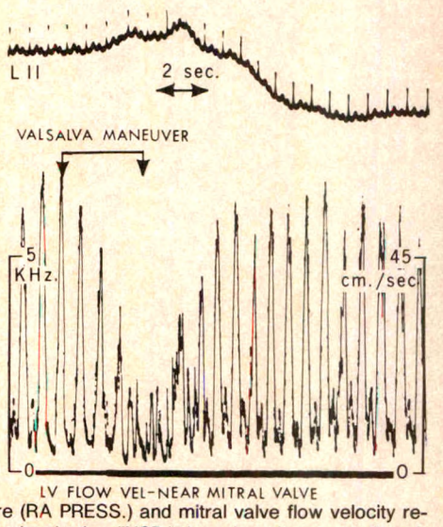


FIGURE 4 (left). Simultaneous lead II of the electrocardiogram (L II), mean right atrial pressure (RA PRESS.) and mitral valve flow velocity recorded in a 28 year old woman with minimal mitral insufficiency during deep respiration. During inspiration (INSP.) there is a decrease of peak mitral valve blood flow velocity and an increase in mean right atrial pressure. During expiration (EXP.), peak mitral valve flow velocity increases when mean right atrial pressure declines.

FIGURE 5 (right). Simultaneous lead II of the electrocardiogram (L II) and mitral valve blood flow velocity recorded in a 28 year old woman with a mild degree of mitral insufficiency. During execution of the Valsalva maneuver, there is a marked reduction of peak mitral valve blood flow velocity. LV = left ventricular; VEL = velocity.

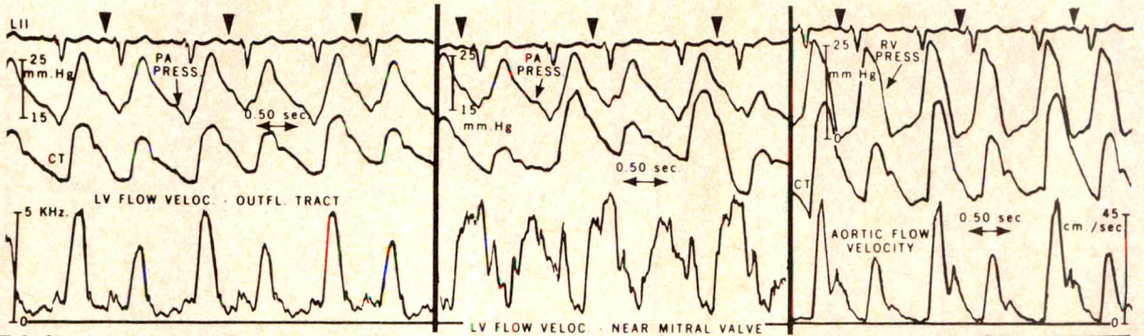
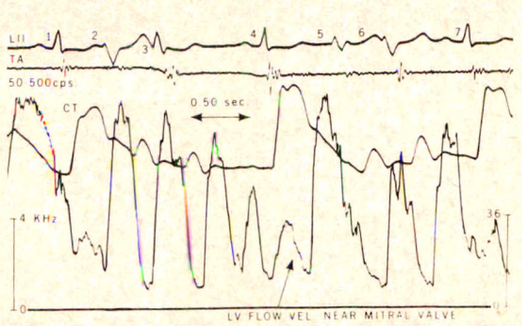


FIGURE 6. Simultaneous recordings of lead II of the electrocardiogram (L II), right heart pressure, external carotid pulse tracing (CT) and blood flow velocity at various sites in a 59 year old woman with essential hypertension and atrial bigeminy. The atrial premature beats are marked by **arrows. Left,** atrial extrasystoles result in reduced pulmonary arterial pressures and decreased amplitude of both external carotid pulse and left ventricular outflow tract blood velocity wave forms. **Middle,** atrial extrasystoles effect reduced peak diastolic mitral valve flow velocities followed by increased systolic components associated with the succeeding sinus beats. **Right,** reductions of peak aortic flow velocity and concordant changes in peak right ventricular (RV) pressures are induced by atrial extrasystoles.



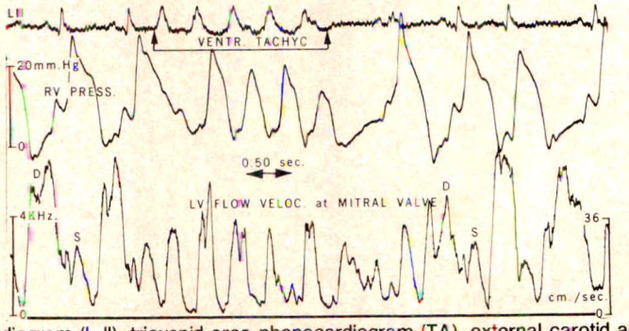


FIGURE 7 (left). Simultaneously recorded lead II of the electrocardiogram (L II), tricuspid area phonocardiogram (TA), external carotid arterial pulse tracing (CT) and mitral valve blood flow velocity in a 54 year old man with coronary artery disease during catheter-evoked ventricular extrasystoles. Ventricular extrasystoles (numbered 2, 3, 5, and 6) result in reduced peak mitral valve blood flow velocity, generally related to extrasystolic coupling intervals. An "overshoot" of peak mitral valve flow velocity and external carotid pulse tracing amplitude during sinus beat 4 is preceded by a longer postextrasystolic interval. LV = left ventricular; VEL = velocity.

FIGURE 8 (right). Simultaneous lead II of the electrocardiogram (L II), right ventricular pressure (RV PRESS.) and mitral valve flow velocity recorded in a 59 year old man with coronary artery disease. During an episode of ventricular tachycardia there is a decline of peak mitral valve blood flow velocity which is paralleled by a reduction in systolic and end-diastolic right ventricular pressure levels. D = diastolic; LV = left ventricular; S = systolic; VELOC. = velocity.

flow velocity reductions related to prematurity of the ectopic beats. Postextrasystolic beats preceded by longer R–R intervals resulted in peak mitral valve flow velocity "overshoot" (Fig. 7). Ventricular tachycardia effected a marked reduction of peak mitral valve flow velocity and the recordings during this arrhythmia were completely irregular. During most beats of the tachycardia, there were concomitant reductions of simultaneously recorded systolic and end-diastolic right ventricular pressures (Fig. 8).

Discussion

The mitral valve diastolic blood flow velocity patterns described here resemble trapezoidal shaped mitral flow wave forms previously recorded in experimental animals by Nolan et al.[1] A continuous blood flow velocity at the mitral valve throughout the cardiac cycle indicates that significant hemodynamic alterations occur at this cavity site during isovolumic relaxation and contraction. The rapid rise of mitral valve flow velocity at the time of the second heart sound may be related to a downward displacement of the mitral valve leaflets before valvular opening. Most descriptions of blood flow profiles at the mitral valves of experimental animals indicate a sharp increase of flow in early diastole.[1,2] During this period, continuing relaxation of the left ventricle and increasing left atrial pressure produce a rapidly rising atrioventricular energy gradient.[3] Careful cineangiographic investigation has also demonstrated major left atrial emptying[14] and left ventricular filling[15] early in the diastolic period.

Left atrial contraction maintains but does not appreciably augment mitral valve blood flow velocity during sinus rhythm. A secondary, smaller acceleration of volumetric mitral flow after atrial depolarization has been noted in animals with implanted ball valve electromagnetic flowmeters,[1] and supplementary left ventricular filling due to atrial contraction is usually no more than 10 to 15 percent of stroke volume.[3] However, Williams et al.,[2] utilizing a flowmeter incorporated into the atrial side of the mitral valve ring in animals, found that peak mitral valve flow occurred at the time of P wave inscription. This latter finding may reflect differences in the anatomic site of flow measurement by various investigators. The sharply inscribed systolic mitral flow velocity wave noted in our study is probably due to left ventricular ejection. However, it is likely that upward movement of the mitral valve during isovolumic contraction[16] results in early systolic reverse flow velocity that is sensed by the flowmeter.

Declining mitral valve flow velocity during exaggerated inspiration and the Valsalva maneuver can be attributed to increased pulmonary arterial blood flow or decreased systemic and pulmonary venous return,[17] which occur during these two respective physiologic maneuvers. The reduction of mitral valve blood flow velocity observed during inspiration can be contrasted with left ventricular outflow tract blood velocity, which increases during this period of the respiratory cycle.[13]

The alterations of mitral valve flow velocity during extrasystoles and ventricular tachycardia are particularly noteworthy. Some experimental evidence[1] suggests that rapid right atrial stimulation reduces mitral forward stroke output and enhances stroke power loss across the valve. This decrease of mitral valve blood flow may be a result of diminished pulmonary venous return, lesser left atrial volumes, reduced left atrial contraction or mitral insufficiency. At present, there are no adequate data in experimental animals with intact mitral valves that might indicate the relative importance of each of these variables. The adverse clinical consequences resulting from diminished mitral valve flow velocity in man during cardiac tachyarrhythmias are evident. Reduced mitral valve flow velocity would effect diminished left ventricular volume and reduce stroke output.

Limitations of the technique: The Doppler flowmeter catheter utilized in our study did not distinguish between forward and reverse flow velocities. It has been demonstrated that a minor degree of net reverse flow does occur in experimental animals[2] and human subjects with intact mitral valves, particularly during isovolumic contraction[2,16] and early diastole.[15] Furthermore, we have recorded substantial net reverse blood flow velocity at the left ventricular inflow tract of man.[18] Currently, the bidirectional Doppler flowmeter cannot be properly maneuvered for positioning at the mitral valve of man as described here.

Advantages of the technique: The Doppler flowmeter catheter is currently the only device that can directly measure phasic instantaneous blood flow velocity at the mitral valve of conscious man. The major advantage of this technique is a capability for characterizing mitral valve flow velocity under a variety of physiologic and pathologic conditions.

Acknowledgment

We acknowledge the technical assistance of Nancy Copeland, RN, Ms. Carole Crevier, Ms. Larry Kuriger, Ms. Sydney Peebles, Ms. Sharon Squire and Mr. Les Zendle.

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Large Dose Furosemide Therapy for Hypertension

Long-Term Use in 22 Patients

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A retrospective study of 22 hypertensive patients receiving large oral doses of furosemide (80 to 640 mg daily for 32 ± 7 months) and standard antihypertensive therapy was performed. All patients had moderately severe or severe hypertension. The substitution of furosemide for the previous diuretic agents resulted in a 22 percent average reduction in arterial pressure and significant improvement in the clinical status of 15 patients. The addition of furosemide allowed a reduction in the dose of antihypertensive medication in four patients. Besides preventing the sodium retention and extracellular fluid volume expansion associated with standard antihypertensive agents, large doses of furosemide may have exerted an additional antihypertensive effect. The combination of orally administered furosemide and standard antihypertensive therapy permitted better control of arterial pressure than that obtained with previous diuretic-antihypertensive combinations in the patients studied. The overall safety of large dose furosemide therapy for extended periods of time appears to be relatively good.

Studies from this laboratory have demonstrated the effectiveness of intravenously administered furosemide as an antihypertensive agent[1] and in the management of congestive heart failure.[2,3] Our experience in a large outpatient population and studies of other workers[4,5] have documented the effectiveness of orally administered furosemide in the management of hypertensive patients. The dose-response curve of furosemide is unusually broad,[6] and the drug is effective in increased doses in the presence of renal insufficiency.[7–10] Relatively few serious side effects have been reported after administration of large doses for short periods[11–14]; however, data are not available on the effectiveness or safety of large doses given for extended periods. Furosemide has been used as a diuretic agent and as an adjunct to antihypertensive therapy in our clinic since 1964. A retrospective analysis of results in patients receiving large dose, long-term furosemide therapy forms the basis of this report.

Methods

A review of the records of patients attending the Hypertension Clinic at the District of Columbia General Hospital revealed that 22 patients had received at least 80 mg of furosemide daily for at least 24 consecutive months. All patients were considered to have essential hypertension on the basis of family history, serum electrolyte determinations and a rapid sequence intravenous pyelogram. All 22 patients were Negro, and 8 were male. The average age was 50 ± 10 years (36 to 70 years). Before initiation of furosemide therapy two patients (Cases 4 and 19) had clinical evidence of congestive heart failure despite digitalization and full doses of antihypertensive and diuretic agents. All patients had electrocardiographic evidence of left ventricular hypertrophy. No patient was uremic; however, six had mild azotemia (blood urea nitrogen 20 to 40 mg/100 ml). Twelve patients had accelerated hypertensive retinopathy (flame-shaped hemorrhages and cotton wool exudates); three of these had papilledema. The remainder of the patients had either grade I or II Keith-Wagener-Barker changes.

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All patients had previously received other diuretic agents for at least 3 months: hydrochlorothiazide, 100 mg daily (13 patients); hydrochlorothiazide, 100 mg, plus triamterene, 200 mg daily (6 patients); hydrochlorothiazide, 100 mg, plus spironolactone, 100 to 250 mg daily (3 patients). They had also received standard antihypertensive agents administered in full doses (methyldopa, 2 g; hydralazine, 300 mg; reserpine, 0.50 mg daily). Furosemide was initially substituted for the previous diuretic agent at a dose of 40 mg twice daily, by mouth. This dose was increased if arterial pressure could not be adequately controlled with the maximal dose of the standard antihypertensive agent, or if the patient had evidence of sodium retention or congestive heart failure. Treatment was continued using the same dose of antihypertensive medication as that previously administered. All patients were receiving a "no added salt diet" which, in the population studied, represents a daily intake of 5 to 10 g of sodium chloride.

Patients were examined in the Hypertension Clinic at weekly, biweekly or monthly intervals. At each clinic visit the patients were questioned as to possible side effects, and body weight was measured. Arterial pressure was determined with a mercury sphygmomanometer with the patient in the sitting position and after 2 minutes of quiet standing. The sitting and standing arterial pressure values from three consecutive clinic visits were averaged and rounded off to the nearest 5 mm Hg. Mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Blood pressure control was deemed adequate if there was at least a 10 percent reduction in mean arterial pressure and the diastolic pressure was maintained at 100 mm Hg or less. Blood for laboratory analysis, by methods described elsewhere,[1] was obtained at biweekly or monthly intervals. Supplemental potassium was administered as a 25 percent potassium chloride solution if the serum potassium level was below 3.5 mEq/liter or if electrocardiographic or clinical signs of hypokalemia were present.

Results

Table I shows the effect of large doses of furosemide and commonly used antihypertensive agents on arterial pressure and weight. The patients were followed up for an average of 32 ± 7 months. Table II shows the various doses of furosemide administered. The average reduction in mean arterial pressure at the end of almost 3 years of this combination therapy was 16 percent (from an average of 193/124 to an average of 163/104 mm Hg). Fifteen patients had decreases in mean arterial pressure ranging from 13 to 46 percent (average 22 percent). The reduction in mean arterial pressure was less than 10 percent in five patients, and two patients (Cases 5 and 12) had net increases in arterial pressure. In four patients (Cases 2, 10, 15 and 19) the substitution of furosemide for the previously used diuretic agent allowed a reduction in the dose of antihypertensive medication. The hypertensive retinopathy markedly decreased in all 12 of the patients with grade III or IV retinopathy (Keith-Wagener-Barker classification), and papilledema disappeared within 2 months (Table III).

The average weight decreased from 202 ± 40 lb to 194 ± 38 lb after 32 months of therapy. Seventeen patients lost an average of 15 ± 11 lb. The initial responses to furosemide therapy were increased diure-

TABLE I

Changes in Weight and Arterial Pressure After Long-Term Large Dose Furosemide and Antihypertensive Drug Therapy

Case no.	Age (yr)	Weight (lb)		Arterial Pressure (mm Hg)	
		Before	After	Before	After
1	59	140	127	170/110	160/90
2	46	210	192	170/120	130/80
3	54	209	220	180/110	200/100
4	70	206	175	180/110	140/100
5	46	265	216	220/130	240/160
6	42	172	166	180/130	115/90
7	45	204	171	230/140	220/120
8	45	260	243	280/165	300/150
9	36	170	153	180/120	170/120
10	38	140	134	160/100	130/90
11	42	188	196	150/120	150/100
12	49	218	229	130/80	140/100
13	41	188	208	160/120	140/100
14	65	163	182	210/120	180/100
15	67	154	147	180/100	150/100
16	55	208	190	180/130	160/90
17	39	239	237	200/130	140/100
18	45	210	204	200/130	140/100
19	65	206	193	240/140	120/80
20	61	233	220	240/140	160/100
21	44	168	157	220/160	170/100
22	39	298	281	180/130	160/100
Ave.	50	202	194	193/124	163/104
SD	±10	±40	±38	±35/19	±42/19

Ave. = average; SD = standard deviation.

TABLE II

Duration and Dosage of Furosemide Therapy

Case no.	Duration (mo) of Daily Oral Dose of Furosemide			Total Duration of Furosemide Therapy (mo)
	80–60 mg	200–320 mg	360–640 mg	
1	13	28	...	41
2	9	5	14	28
3	22	15	...	37
4	40	7	...	47
5	8	2	16	26
6	7	5	19	31
7	4	1	21	26
8	10	1	14	25
9	3	...	18	21
10	7	6	12	25
11	2	27	12	41
12	29	17	...	46
13	16	12	1	29
14	13	31	...	44
15	3	6	22	31
16	3	3	20	26
17	...	26	...	26
19	8	16	...	24
20	3	33	...	36
21	12	15	...	27
22	23	9	...	32

TABLE III

Clinical Characteristics of Patients Before and After Large Dose Furosemide and Antihypertensive Therapy

	Patients (no.)	
	Before	After
Congestive heart failure	2	0
Left ventricular hypertrophy by electrocardiogram	22	22
Azotemia	6	3
Retinopathy*		
Grade IV	3	0
Grade III	9	2
Grade II	8	18
Grade I	2	2

*Keith-Wagener-Barker classification.

TABLE IV

Laboratory Studies After Long-Term Large Dose Furosemide and Antihypertensive Therapy (mean values in 22 patients treated for 32 months)

	Before	After
Hematocrit	38 ± 5	41 ± 5
Blood urea nitrogen (mg/100 ml)	21 ± 7	21 ± 12
Fasting blood glucose (mg/100 ml)	94 ± 34	101 ± 25
Sodium (mEq/liter)	143 ± 4	142 ± 3
Potassium (mEq/liter)*	4.0 ± 0.4	3.9 ± 0.4
Uric acid (mg/100 ml)	7.8 ± 2.4	10.3 ± 2.2
SGOT (units/ml)	14 ± 6	16 ± 8
Alkaline phosphatase (Bessy-Lowry units)	1.5 ± 0.6	1.9 ± 0.8

*Five patients received supplemental potassium during furosemide therapy.

SGOT = serum glutamic oxaloacetic transaminase.

sis, weight loss and, in 2 patients, clearing of congestive heart failure. Although no patient had clinical evidence of sodium retention, it was necessary to increase the dose of furosemide to more than 80 mg/day to maintain adequate control of arterial pressure in all patients. With subsequent increases in dose, the potentiation of the antihypertensive effect was repeatedly noted; however, weight loss and diuresis were not consistent and did not appear to be related to the antihypertensive response. No differences in antihypertensive response were noted between men and women.

Table IV shows the effect of furosemide on blood chemistry values. There were no significant changes except for an increase in uric acid observed in all 22 patients. Three patients (Cases 6, 8 and 11) had an average increase of 18.5 mg/100 ml in blood urea nitrogen; however, three others (Cases 4, 19 and 21) had an average decrease of 14.2 mg/100 ml. Two patients had diabetes mellitus before institution of furosemide therapy; one of them required an increased dose of orally administered hypoglycemic agents. In addition, three patients who had no history of diabetes manifested clinical diabetes while receiving furosemide therapy. The condition of these patients was controlled with diet and orally administered hypoglycemic agents. Five patients (Cases 3, 5, 11, 18 and 21) required supplemental potassium administration because of a serum potassium level below 3.5 mEq/liter. No patient had symptoms of hypokalemia.

Discussion

Despite maximal doses of antihypertensive agents and diuretic agents, the arterial pressure of the patients studied was inadequately controlled before treatment with furosemide. The substitution of furosemide for the previous diuretic agent permitted adequate control of arterial pressure in 15 patients; in 4 of these patients control of arterial pressure was accomplished with reduced doses of antihypertensive agents. Seven patients had no significant improvement in arterial pressure or clinical status although there was no obvious clinical difference between these patients and the 15 who responded to therapy.

Mechanism of beneficial effects of furosemide therapy: Data from previous studies in our laboratory may help to explain the beneficial effects of furosemide in these patients. Most antihypertensive drugs have sodium-retaining properties that can be associated with expansion of the plasma and extracellular fluid volumes, and these volume changes may account for either decreased responsiveness to antihypertensive agents or the development of apparent drug resistance.[15] It is possible that the large doses of antihypertensive agents administered to the patients in this study necessitated the increased doses of furosemide to overcome this effect. It seems logical to hypothesize that the previously administered diuretic agents were not potent enough to prevent the sodium retention caused by the maximal doses of the antihypertensive agents. The potency of furosemide and its increased potency in larger doses blocked the sodium-retaining properties of the antihypertensive agents, thus allowing the latter to exert their full antihypertensive effect. Recent studies by Dustan et al.[16] emphasize the importance of precise volume control in maintaining blood pressure reductions during antihypertensive treatment.

During the initial stages of furosemide therapy, all patients lost weight (average 4.5 ± 2.1 lb during the first week of therapy). This initial weight loss was thought to represent diuresis and loss of body fluids. The weight change over the remaining 32 months could not be entirely accounted for by a net fluid loss and probably represented changes in caloric balance. When furosemide is given intravenously, its antihypertensive effects are unrelated to weight loss and diuresis.[1] In this study we repeatedly noted that subsequent increases in the dose of furosemide resulted in an additional antihypertensive effect that was apparently unrelated to either diuresis or weight loss. This

antihypertensive action usually occurred with oral doses of 200 to 600 mg daily. Our findings are in agreement with those of Hutcheon and Leonard,[4] who observed that the antihypertensive action of orally administered furosemide in doses of 100 to 200 mg daily was independent of diuresis. The mechanism of this antihypertensive action of large doses of furosemide could have been related to changes in fluid volume or to a decrease in cardiac output, as originally postulated by Wolfer et al.,[17] since these variables were not measured in our study. The possibility exists that the large doses of furosemide had an antihypertensive action independent of diuresis, as found by Hutcheon and Leonard,[4] since there was no change in body weight on a week to week basis when the dose of furosemide was increased to more than 100 mg daily.

Side effects: Although the average value for blood urea nitrogen did not change in the 22 patients, an increase was noted in 3. Investigation of this azotemia revealed no pre- or postrenal origin, and this deterioration of renal function was thought to represent progression of the underlying hypertensive disease process. A rise in serum uric acid levels was noted in all patients. Four patients were receiving probenecid before furosemide therapy and in two additional patients, clinical gout developed during the study. In one of the two patients with known diabetes it was necessary to increase the dose of tolbutamide from 1 g daily to 2 g daily. Clinical diabetes, which became apparent in three other patients receiving furosemide therapy, was effectively treated with diet and 500 mg of tolbutamide administered twice daily. It is not known if the previous administration of thiazide diuretic agents or the large doses of furosemide alone accounted for the high rate of diabetes mellitus in these patients. Therefore, in addition to monitoring of serum electrolytes and blood urea nitrogen, it seems advisable to monitor blood glucose levels at frequent intervals in patients receiving large doses of furosemide.

Clinical implications: Our study demonstrated that large doses of furosemide (80 to 640 mg daily) administered over 2 1/2 years produced no toxic effects and had side effects similar to those of thiazide diuretic agents (hypokalemia, hyperglycemia and hyperuricemia). When combined with standard antihypertensive agents, furosemide not only prevents their sodium-retaining properties, thus allowing them to exert their full effect, but also may exert an additional antihypertensive effect. The combination of standard antihypertensive agents with large doses of furosemide appears to permit better control of arterial pressure than that obtained with other diuretic-antihypertensive combinations in patients with moderately severe or severe hypertension.

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Experiments on the Mitral Valve (Stricker, 1883)

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At present it can be discerned that, from the viewpoint of historical development, cardiac surgery is a composite of techniques variously applied to various components of the heart, these techniques having markedly different origins.

Surgery of the valves originated with 19th century European physiologists and pathologists, such as Julius Cohnheim (1839–1884), Edwin Klebs (1834–1913) and Ottomar Rosenbach (1851–1907), who was Cohnheim's pupil. Their contributions have been discussed in previous issues of this Journal.[1–4]

Directly in the line of development is Salomon Stricker (1834–1898), a student of histology, experimental pathology and philosophy. The following excerpts have been translated from Stricker's Vorlesungen über Allgemeine und Experimentelle Pathologie (Lectures on General and Experimental Pathology, Vienna, Braumüller, 1883, pp. 805 ff). This book is dedicated to Carl von Rokitansky, the illustrious Austrian pathologist.

Excerpt from Stricker's Lecture

Let us now illustrate the conditions as they shape themselves in some pathological states of the heart. Let us posit the case that the atrioventricular valves—specifically the mitral valve—are insufficient.

With normal atrioventricular valves the intracardiac pressure begins to rise with the onset of systole. According to dominant doctrine it must increase until it is able to overpower the aortic pressure and open the semilunar valves.

If the mitral valve suddenly becomes insufficient, in the moment in which the ventricle begins to become smaller the blood must be shunted toward the atrium, where the pressure normally is much lower than in the aorta.

If the exit through the atrioventricular orifice were large enough to let the blood be shunted to such a degree when the ventricle becomes smaller, one would have to surmise that the semilunar valves do not open until the pressure in the left atrium is greater than the pressure in the aorta and that the ventricular blood encounters less resistance at the semilunar valves than at the atrioventricular ostium and left atrium.

This study was based on research assisted by the National Institutes of Health (Grant HL-10948).

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This speculation was aroused by a chance observation. In the course of their comparative investigations on the pressures in the two circulations, Openchowsky and Wagner on one occasion came upon an animal in which the pressure in the pulmonary artery was somewhat higher than in the aorta. The autopsy revealed the presence of mitral insufficiency. Now if in certain degrees of mitral insufficiency the pressure in the pulmonary artery were actually greater than that in the aorta, one would have to surmise that the pressure in the left atrium also was abnormally high and that during systole in the moment in which a new quantum of blood is thrown into the atrium, the pressure there rises as much as is necessary to open the semilunar valves.

The symptom complex that is observed in cases of mitral insufficiency is not incompatible with this hypothesis. The hypertrophy of the right ventricle and the accentuation of the second heart sound at the pulmonic area make us suspect elevation of pressure in the lesser circulation.

Skoda, the discoverer of accentuation, has also evaluated this phenomenon in the same way. On the other hand, in severe mitral insufficiency the arterial pulse is usually small and easily compressible.

Thus, when the clinical evidence allows one to surmise that the pressure in the pulmonary artery rises and the aortic pressure falls, it would be admissible to suspect that that chance observation in a dog corresponds to the state of affairs in mitral insufficiency. Meanwhile a correctly arranged experiment did not give the expected answer to the questions that have been raised here.

When I open the thorax of a large dog by resecting a few ribs on the left side, I can very readily introduce a suitable cannula* through the left auricle and advance it into the ventricle. Then I tie it to the auricle so as to make the communication between ventricle and atrium continuous. After the introduction and attachment of a cannula of this kind, you can see how the atrium and auricle fill with each ventricular systole. By placing a finger over the left atrium you can also feel a distinct whirr, a sure sign that the ventricle is discharging part of its contents into the atrium.

In one instance the experiment gave the following result. Before the insufficiency was produced, the pressure in the pulmonary artery was very low (about 20–25 mm of mercury); the pressure in the aorta was 160. Now the staying power of the left ventricle was tested by interruption of respiration. After this test the aortic pressure sank to 110 mm during regular respiration. Now the insufficiency was produced. The aortic pressure fell another 40 mm; naturally, I

* The cannula is provided with several holes at its sides; the end can be occluded by a tap.

cannot tell whether this was due to the insufficiency or to bad handling of the ventricle. The pressure in the pulmonary artery did not rise. The recording was continued for an additional 15 minutes. At the end of the experiment the pressure in the pulmonary artery was about as high as at the beginning. After the insufficiency was established I interrupted the respiration once more. The pressure in the aorta rose to 180 mm in 40 to 50 seconds. There was a scarcely perceptible elevation of pressure in the pulmonary artery.

In the few experiments which I have carried out after this one, the conditions were not always the same. For example, in one experiment, after the establishment of insufficiency the aortic pressure was not higher than the pulmonic.* With the interruption, however, the aortic pressure rose very considerably; thus conditions were produced such as I have already described.

In the last mentioned experiment in the presence of low aortic pressure the whirr (the systolic backflow of blood into the atrium) was very weak; it became distinctly stronger when the aortic pressure increased. Thus the regurgitating stream must increase with increasing aortic pressure. This fact is especially important.

We know that, especially in mild cases, mitral insufficiency is well tolerated as long as the patient leads a quiet life but that when any strenuous work is performed—e.g., stair-climbing—dyspnea and palpitation occur. Patients who have severe insufficiency do relatively well only when they are in bed; even walking about in the bedroom arouses agitation of the heart.

What is the reason for this?

I stated previously that every muscular action is associated with elevation of blood pressure. In mitral insufficiency the causes of the elevation do not cease, since the elevation is dependent on contraction of the small blood vessels. But the task of the ventricle increases when the mitral valve is insufficient, in another relation than exists when the valve is normal. When the aortic pressure is increased, the opening of the semilunar valve becomes more difficult and the blood regurgitates in greater amount against the *locus minoris resistentiae,* i.e., into the atrium. Indeed it would flow there entirely if there were not some sort of compensation, by which the semilunar valve is nevertheless opened. But of what does this compensation consist? For the present I can only answer speculatively.

I have here a model in which the heart is represented by a rubber ball. This ball is open at two sides. On one side it leads to a system of tubes equipped with a manometer. This opening has a valve which opens the way the semilunar valve opens, i.e., toward the system of tubes. By means of a screw I can regulate the outflow from the system of tubes. I can make it narrower or wider and I can close it off altogether. In this way I can imitate the changes in the lumina of the small arteries. The other opening of the ball leads to a reservoir. This opening has no valve. The reservoir represents the atrium together with the lesser circulation, against which the ventricle has no valve—i.e., even less than an insufficient valve.

Now when I squeeze the ball rhythmically in imitation of ventricular systoles, I drive the water, which is dyed blue and which fills my reservoir and the balloon, into the blindly† ending system of tubes until it is itself under a certain pressure. As soon as this pressure has been reached, no more fluid passes into the system of tubes. Compression empties the balloon just as before, but the fluid goes back into the reservoir. However I can also drive fluid immediately into the system of tubes when I compress the ball more quickly than before. If I increase the speed of compression I also increase the filling of the system of tubes despite the continually increasing pressure, despite the insufficiency or despite the open communication with the reservoir, which is under lower pressure.

Doubtless in the heart with an insufficient mitral valve the same possibility exists of driving the blood into the aorta despite the fact that a much higher pressure prevails there than in the atrium. By turning speed into pressure the ventricle must only contract with corresponding speed in order to produce the pressure necessary to open the semilunar valve.

In this work, however, a greater task is imposed on the heart. When the pressure suddenly rises further, the ventricle must contract more rapidly in order to be able to open the semilunar valves. In the presence of this greater task quicker exhaustion is intelligible.

The experimental study that I have reported on this occasion concerns only insufficiency that arises acutely; there can be no question of compensation such as is found in man. When we find hypertrophy of the right heart in the presence of mitral insufficiency and, still more distinctly, in the presence of stenosis of the left atrioventricular orifice, this hypertrophy is doubtless the sequel of prolonged restriction of the outflow of blood from the lesser circulation.

Meanwhile I have noticed, not unintentionally, that 15 minutes after establishment of the insufficiency the pressure in the pulmonary artery has not yet risen. This experiment, I wish to suggest, gives us no conclusion as to how rapidly complications and compensations go into effect.

Physicians assert that insufficiency which takes onset acutely can quickly lead to death. Experiment gives us no conclusion as to this also. From the course of the pressure curve in the first 15 minutes after the establishment of insufficiency it cannot be inferred that the circulation must become fatigued. Hence it is permissible to surmise that in cases in which insufficiency arising acutely leads rapidly to death, the fatal result is caused not by insufficiency alone but by other complications. For example, when myocarditis is present and the heart muscle cannot permanently cope with the new burden that is put upon it by the insufficiency, a cause of death might very well be present. Large masses of exudate in the pericardial cavity might also act in the same way as myocarditis, inasmuch as they make pressure against the muscle of the heart and the heart cannot dilate when it is burdened by external pressures.*

Comment on Excerpts from Stricker

The foregoing passages, a small excerpt from a large book, contain several aspects that deserve comment. We notice first that knowledge of physiology had reached a degree of development such that it had become possible to consider the functions of individual chambers of the heart and to study these func-

* In this instance the pressure was very low before the insufficiency. In addition, the communication between the ventricle and the atrium was very wide, since I had modified the cannula.

† I draw the blind end through the screw-clamp; this is useful for the present experiment.

* For the heart of the frog Morro and Pagliani have shown that a pressure of 20 cc of water is sufficient to prevent diastolic filling. Francois-Franck introduced fluid into the pericardial cavity under slight pressure and found that very important deleterious effects occurred, e.g., diminution of the arterial pressure and elevation of the venous pressure.

tions quantitatively. Unlike some of the earliest workers who had been content to measure carotid arterial pressures alone during experiments on valves, Stricker made simultaneous determinations of pressure in the pulmonary artery and aorta. Second, it is observable that clinical reasoning had attained a comparable degree of sophistication, as is shown by the remarks about the pathogenesis of pulmonic accentuation.

We may notice also that Stricker's observations on canine cardiac physiology were made with constant reference to conditions found in human disease. For example, Stricker was obviously aware that in mitral disease of intermediate severity the patient is tolerably comfortable at rest but readily becomes dyspneic on exertion. He also was familiar with the clinical picture produced by myocarditis and with that produced by large pericardial exudates.

It is further of interest that Stricker illustrated his lecture by means of a rather elaborate model, consisting of a rubber ball, tubes, valves and a reservoir. These models have a long history, in association with which we might mention the names of von Basch and MacCallum. It is even possible that something similar may be traceable in the writings of the iatrophysicists who followed Galileo.

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Paroxysmal Atrioventricular Block Related to Phase 4 Bilateral Bundle Branch Block

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Repeated episodes of paroxysmal atrioventricular (A–V) block were recorded from a 78 year old woman with Stokes-Adams seizures. After a single or occasionally two consecutive and conducted atrial extrasystoles, all the succeeding P waves were blocked. Normal A–V conduction was resumed only when a P wave fell within a certain time interval after a ventricular escape beat. Three A–V conduction phases were identified: an early phase of A–V block, a late phase of A–V block and an intermediate phase during which A–V conduction was preserved. Within the phase of preserved A–V conduction, three intraventricular conduction subphases were found: an early phase of incomplete left bundle branch block, an intermediate phase of normal intraventricular conduction (mixed with incomplete right bundle branch block) and a late phase of high grade right bundle branch block. Thus, conduction was initially impaired more or only in the left bundle and, as the R–P intervals increased, conduction deteriorated progressively in both bundle branches but at a higher rate in the right bundle, until conduction failed totally in both bundle branches. This case, a complex variant of paroxysmal A–V block, seems to be the first reported instance of enhanced diastolic depolarization occurring in both bundle branches simultaneously and giving rise to phase 4 bilateral bundle branch block.

Phase 4 paroxysmal atrioventricular (A–V) block is a variety of A–V block in which normal A–V conduction is suddenly interrupted whenever an atrial impulse falls relatively late in diastole.[1] Normal A–V conduction is reestablished only after a ventricular escape beat, provided a P wave falls within a limited interval immediately after this beat. This form of A–V block has been related to the existence of hypopolarization and spontaneous diastolic depolarization in one population of cells of the affected fascicle. However, another population of cells may show prolonged recovery, giving rise at the same time to phase 3 A–V block.[1] Thus, in such cases two phases of A–V block tend to occur: an early phase of tachycardia-dependent or phase 3 block and a late phase of bradycardia-dependent or phase 4 block. Normal A–V conduction occurs between these phases.[1] In most cases, the paroxysmal A–V block is precipitated by sinoatrial slowing when a delayed P wave falls late during phase 4 block. In some cases, the paroxysmal A–V block is triggered by a premature beat when the postextrasystolic P wave falls sufficiently late. Most commonly, the lesions responsible for the paroxysmal A–V block occur in one bundle branch when there is total interruption of conduction in the contralateral branch.[1]

In this report we analyze a case of paroxysmal A–V block in which hypopolarization and spontaneous diastolic depolarization seemed to occur simultaneously in both bundle branches. This event gave rise, in addition to paroxysmal A–V block precipitated by atrial extrasys-

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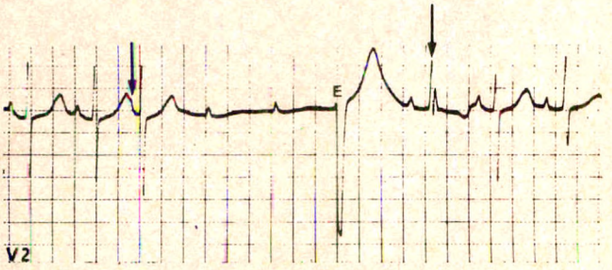

FIGURE 1. Typical episode of paroxysmal A–V block. The first two beats show 1:1 A–V conduction, with a P–R interval of 0.16 second and a normal QRS configuration. An atrial extrasystole **(first arrow)**, with an R–P interval of 0.28 second is conducted with a P–R interval of 0.10 second and a pattern of incomplete left bundle branch block. The next two P waves are blocked and, after an interval of 1.76 seconds, an escape beat (E) occurs (with a pattern of left bundle branch block) and 1:1 A–V conduction is reestablished. The first beat after the escape beat shows high grade right bundle branch block **(second arrow)**.

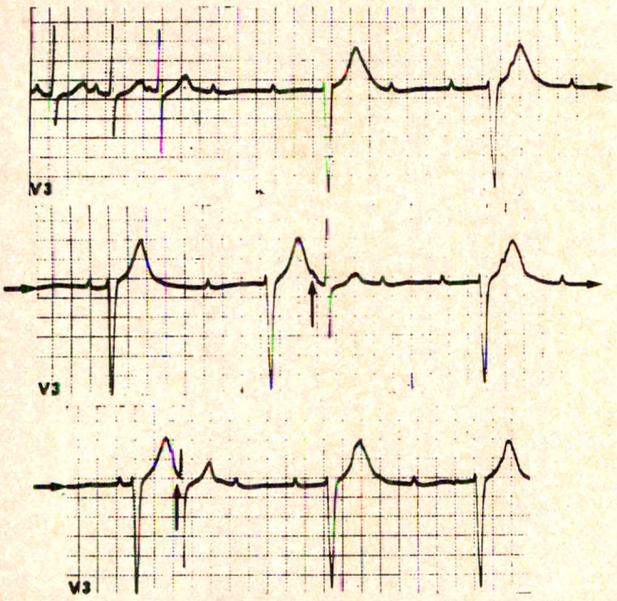

FIGURE 2. Episode of paroxysmal A–V block of longer duration. The three strips are continuous. The A–V block is preciptated by a single atrial extrasystole (third beat). All the P waves are blocked, except for two **(arrows)** that fall at an appropriate distance after the idioventricular beats.

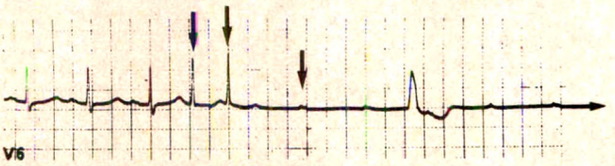

FIGURE 3. Paroxysmal A–V block precipitated by two consecutive atrial extrasystoles. The first three beats are of sinoatrial origin, with 1:1 A–V conduction. Then, two atrial extrasystoles occur **(arrows)**, the first, with an R–P interval of 0.32 second, and the second, with an R–P interval of 0.28 second. Both are conducted with a short P–R interval of 0.13 second. The paroxysmal A–V block begins with the first postextrasystolic P wave **(third arrow)**.

toles, to a complex array of conducted impulses showing different degrees of right or left bundle branch block with different degrees of prolongation of the P–R interval.

Report of Case and Analysis of Electrocardiograms

A 78 year old woman was hospitalized because of Stokes-Adams seizures of short duration, which had started 4 days previously. No other clinical or laboratory abnormalities were present. A long electrocardiographic tracing revealed a sinoatrial rhythm with a rate of approximately 100/min, a changing P–R interval and a QRS complex with a pattern ranging from normal to incomplete right bundle branch block. In addition, there were atrial extrasystoles, most of which precipitated episodes of paroxysmal A–V block. Twenty episodes were recorded and, with slight variations, all began and ended in the same way. Figures 1 to 3 illustrate three episodes. In Figure 1, the paroxysmal A–V block is precipitated by an atrial extrasystole that is conducted to the ventricles with a pattern of incomplete left bundle branch block (first arrow). The block is of short duration because A–V conduction reestablished in the first P wave after the first escape beat. The first beat reestablishing A–V conduction shows a pattern of right bundle branch block (second arrow). In Figure 2 the paroxysm is also provoked by a single atrial extrasystole, but is of longer duration because the P waves after the escape beats are not conducted except for the two marked by arrows. In Figure 3 the episode is triggered by *two* consecutive atrial extrasystoles, both conducted (first two arrows). This figure demonstrates that, if it is sufficiently late, the P wave after an atrial extrasystole actually initiates the paroxysmal A–V block. In all the episodes, whenever a single P wave is

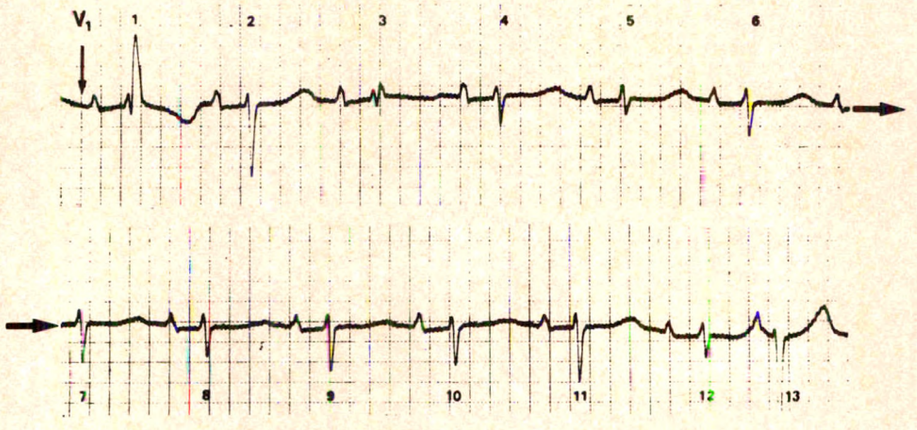

FIGURE 4. Different types of intraventricular conduction. The two strips are continuous and were recorded at a paper speed of 50 mm/sec and with a calibration of 20 mm/mv. Beat 1 shows a high degree of right bundle branch block; beat 3 shows a lesser degree, and beats 4, 5 and 12 a still lesser degree, which can only be recognized by comparison with the normal beats (6 to 10). Beats 2 and 13, and perhaps also beat 11, show different degrees of incomplete left bundle branch block.

blocked, all the succeeding P waves are also blocked. Figures 1 to 3 also show that all the P waves that fall either early or late after the escape beats are blocked, whereas P waves falling at an intermediate distance are conducted. The QRS configuration of the conducted beats varies according to the atrial rate or the coupling of the premature impulses or the R–P interval after the escape beats. Thus, several different QRS patterns, ranging from normal to different degrees of right and left bundle branch block, can be observed in a single tracing (Fig. 4).

The P–P, R–R, P–R and R–P intervals were measured and the latter were correlated with both atrioventricular and intraventricular conduction (Fig. 5). The most important findings were as follows: (1) All atrial impulses with an R–P interval shorter than 0.28 second were blocked (first arrow). (2) Atrial impulses with an R–P interval of 0.28 to 0.40 second were conducted to the ventricles with a relatively short P–R interval (0.10 to 0.14 second) and a pattern of incomplete left bundle branch block (second arrow). (3) Atrial impulses with an R–P interval of 0.41 to 0.48 second were also conducted, but with an average P–R interval of 0.165 second and a QRS pattern varying between normal and incomplete right bundle branch block (third arrow). (4) Atrial impulses with an R–P interval of 0.50 to 0.68 second were conducted with an average P–R interval of 0.18 second and a pattern of high grade or complete right bundle branch block (fourth arrow). (5) Some atrial impulses with an R–P interval of 0.56 to 0.68 second and all atrial impulses with an R–P interval greater than 0.68 second were again totally blocked (fifth arrow).

Ranges of A–V conduction: Figure 5 shows that both early and late atrial beats were blocked; intermediate atrial impulses were conducted to the ventricles. Thus, three A–V conduction phases were present: (1) a phase of early A–V block (black bar to the left), (2) a phase of late A–V block (black bar to the right), and (3) an intermediate phase of preserved A–V conduction (white bar). This distribution is similar to that described in paroxysmal A–V block[1] as well as in intermittent bundle branch block,[2] thus suggesting participation of the same electrophysiologic mechanisms. Accordingly, the black bar to the left corresponds to phase 3 block, and the black bar to the right corresponds to phase 4 block.[1,2] Moreover, an "accordion effect" which so well describes the fact that the two phases of block seem to compress the intermediate conduction range has also been

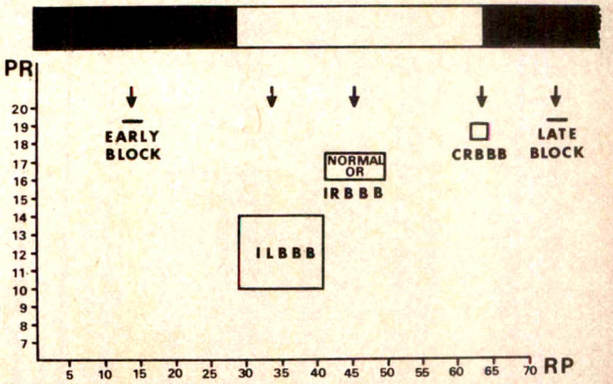

FIGURE 5. Relation between R–P **(abscissa)** and P–R intervals **(ordinate)**, in hundredths of a second. Total A–V block occurs after the shortest **(first arrow)** and after the longest **(fifth arrow)** R–P intervals. In addition, the R–P intervals are correlated with the type of intraventricular conduction. CRBBB = high grade or complete right bundle branch block; ILBBB = incomplete left bundle branch block; IRBBB = incomplete right bundle branch block. The **bar** at the top represents the accordion effect. See text.

documented.[1–3] The difference in the present case was that, during the intermediate phase of A–V conduction, the P–R intervals were not constant and increased slightly and progressively from left to right.

In addition, within the intermediate phase of A–V conduction, three subphases could be demonstrated: (a) an early phase of incomplete left bundle branch block, (b) an intermediate phase of normal intraventricular conduction intermingled with incomplete right bundle branch block, and (c) a late phase of high grade or complete right bundle branch block. These three subphases coincided with a progressive increase of the P–R interval. Thus, it appeared that initially A–V conduction was impaired only or more in the left bundle; thereafter, conduction deteriorated progressively in both bundle branches, but more rapidly in the right bundle, until conduction was totally interrupted in both bundle branches.

Ranges of intraventricular conduction: Figure 6 represents an attempt to explain these conduction abnormalities in terms of recovery of excitability and impulse propagation or the possible configuration of the action potentials of the injured fibers in the bundle branches. Thus, early or

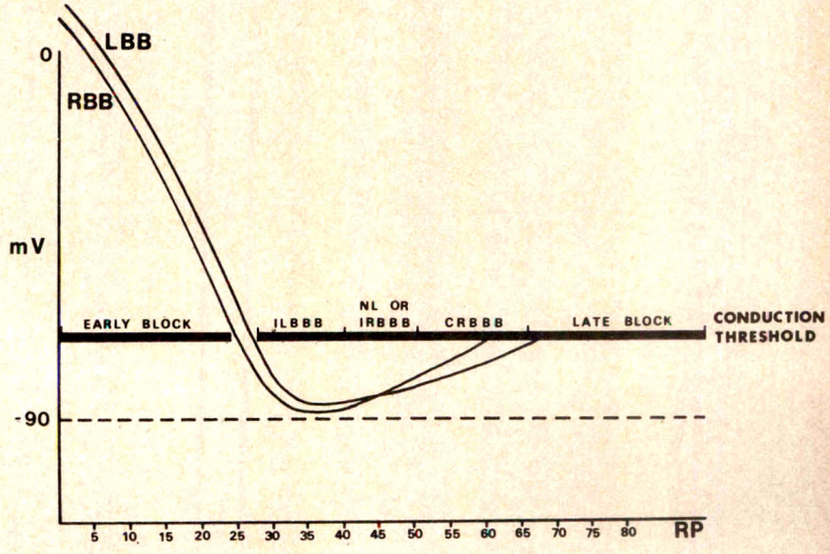

FIGURE 6. Diagrammatic representation of the findings of Figure 5. RBB and LBB represent the recovery curves of the right and left bundle branch, respectively. The two bundle branches are assumed to be hypopolarized and to show an increased rate of diastolic depolarization. The slope of diastolic depolarization is steeper in the right than in the left bundle branch. The **horizontal bar** designated "conduction threshold" corresponds to the critical level of transmembrane potential that separates conduction from total block, during both repolarization and diastolic depolarization. R–P intervals and phases of atrioventricular and intraventricular conduction as in Figure 5. See text.

phase 3 A–V block was related to incomplete recovery in both bundle branches, whereas late or phase 4 A–V block was related to enhanced diastolic depolarization, also in both bundle branches. The subphase of incomplete left bundle branch block was attributed to the duration of the recovery period, which was slightly longer in the left than in the right bundle. The subphase of right bundle branch block was attributed to the slope of diastolic depolarization, which was steeper in the right than in the left bundle. The subphase of normal intraventricular conduction probably corresponded to the moment when the two curves tended to overlap. The beats showing incomplete left bundle branch block were accompanied by an extremely short P–R interval, thereby suggesting that recovery in the right bundle was complete at that moment. The occurrence of only incomplete left bundle branch block of slight degree indicated that recovery in the left bundle was nearly complete. The fact that the P–R interval increased progressively along the A–V conduction range suggested that diastolic depolarization began to increase very early in both bundle branches.

Discussion

Our present case is a peculiar variant of phase 4 paroxysmal A–V block. As in all previously reported cases,[1] the A–V block began when an atrial impulse fell late in diastole; A–V conduction was reestablished only after an escape beat. The basic electrophysiologic mechanisms were also well represented by an accordion effect, with an early or phase 3 A–V block, late or phase 4 A–V block, and an intermediate A–V conduction phase. However, whereas in all previous cases[1] the intermediate phase was a range of *normal* A–V conduction with a constant P–R interval and QRS pattern, in our case it was a phase of *preserved* A–V conduction, during which the P–R interval increased gradually and the QRS pattern changed successively from one of incomplete left bundle branch block to normal, then to incomplete right bundle branch block and finally to high grade right bundle branch block.

In previous cases,[1] paroxysmal A–V block occurred when prolonged recovery, hypopolarization and enhanced diastolic depolarization took place in one fascicle in the presence of total interruption of the remaining fascicles: hence, an intraventricular conduction system was abnormally transformed into a "monofascicular" system. In our present case, these alterations occurred at the same time in the two main bundle branches, and no fascicle was totally interrupted. Thus this case has important academic value. Indeed, if the described physiologic abnormalities could occur in one single fascicle, it was natural and even necessary that they could occur simultaneously in both bundle branches. Thus, our case is a necessary link in the chain of suggested mechanisms.[1,2]

In paroxysmal A–V block, the critically injured region responsible for the A–V block has almost invariably been infranodal.[1] The same was true in our present case; moreover, the occurrence of phase 4 right and left bundle branch block in the same patient gave rise to a peculiar variety of bilateral bundle branch block. All previously reported cases of bilateral bundle branch block were examples of phase 3 block.[4] The present case seems to be the first reported example of "phase 4 bilateral bundle branch block."

Although phase 4 block was clearly present in both bundle branches, there was less certainty about phase 3 block. Thus, although the early phase of A–V block was attributed to incomplete recovery in both bundle branches, it is possible that early atrial impulses were blocked in the A–V node. In addition, even if recovery was prolonged, the prolongation was necessarily slight. This is not surprising since in this type of process the greater the injury and hypopolarization, the shorter can be the action potential duration.[1,2] Perhaps for this reason many of the atrial extrasystoles were readily conducted to the ventricles (Fig. 3).

Injury seemed to be slightly greater in the right than in the left bundle for the following reasons: (1) The slope of diastolic depolarization was steeper in the right bundle and, probably for the same reason, the escape beats showed a left bundle branch block pattern (Fig. 1 to 3), thus suggesting a possible site of origin of escape and ectopic beats in the critically injured area of the right bundle. (2) Recovery was completed first in the right bundle. (3) The spontaneous diastolic depolarization seemed to start earlier in the right bundle; however, injury was also important in the left bundle since both depolarization slopes began and reached critical levels for total block very early.

When diastolic depolarization is enhanced, ectopic beats and reentry may occur, although not always and not necessarily. In another report[5] we analyze why increased automaticity and depressed conduction (which are so commonly interrelated) may become dissociated or demonstrate a lack of synchrony.

The gradual increase in the P–R interval during the phase of preserved A–V conduction is interesting because this progression may draw a parallel to the slope of diastolic depolarization, and because it was not seen in other clinical cases of paroxysmal A–V block.[1] However, such progression has been documented in paroxysmal A–V block provoked experimentally in the canine heart (unpublished observations).

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Aneurysm of the Left Atrium

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Congenital left atrial aneurysm is a rare anomaly that has been reported only five times previously. The usual presenting features include an abnormal chest roentgenogram, an apical systolic murmur and supraventricular tachycardia. Even with cineangiocardiography the diagnosis is uncertain, and the lesion is commonly confused with cardiac tumor. Aneurysmectomy is the preferred treatment and has been successful in all patients undergoing operation. The presence of thrombi in the aneurysm necessitates circulatory assistance during excision.

Aneurysms of the left atrium may be congenital or acquired in origin. They are considered congenital when no predisposing cardiac condition is present. Acquired aneurysms may be secondary to rheumatic mitral insufficiency or stenosis, tuberculosis, syphilitic myocarditis or other conditions leading to abnormal atrial pressures or weakened myocardium.[1–5] Congenital aneurysms involve either the atrial wall (left atrial aneurysm) or the appendage of the atrium (left atrial appendage aneurysm). Five cases of the former[6–10] and 11 of the latter have been recorded.[11–19] Aneurysms of the left atrial appendage are often associated with a pericardial defect and, although more common, are probably of less significance. Since the case to be presented is that of an aneurysm of the left atrial wall, discussion will be limited to this type of lesion.

Case Report

The patient, a 13 year old girl, presented initially at age 1 year with congestive heart failure. Cardiomegaly was noted on the chest roentgenogram, and the electrocardiogram showed left atrial and left ventricular hypertrophy. Cardiac catheterization and angiocardiography revealed a large left atrium with no associated valvular or septal defects. Diminished cardiac pulsations were observed. The diagnosis could not be established with certainty, but it was presumed that the child had endocardial fibroelastosis.

The heart failure responded to decongestive measures, and the patient's condition remained stable for several months. However, because of persistent cardiomegaly and exercise intolerance, cardiac catheterization was repeated at age 2 years. A large left atrium was again demonstrated, but this time overt mitral insufficiency was present. Although the patient's clinical condition remained satisfactory, a reassessment of her cardiac status at age 9 was believed indicated. The previous findings were confirmed with no new observations. It was elected to discontinue administration of digoxin at that time.

One year later the patient complained of episodes of palpitation followed by syncope. She was hospitalized, and supraventricular tachycardia was documented. The arrhythmia responded promptly to treatment with digoxin, and she was discharged on maintenance dosage. There were numerous recurrent episodes of arrhythmia (atrial fibrillation and supraventricular tachycardia) and in four instances, these were severe enough to require hospitalization. These were treated by adjusting the dose of digoxin and adding oral propranolol.

At age 13 years, calcification in the area of the mitral valve was observed on roentgenogram (Fig. 1) which, in retrospect, could be seen in the films obtained 4 years previously. She was admitted to the hospital for further evaluation.

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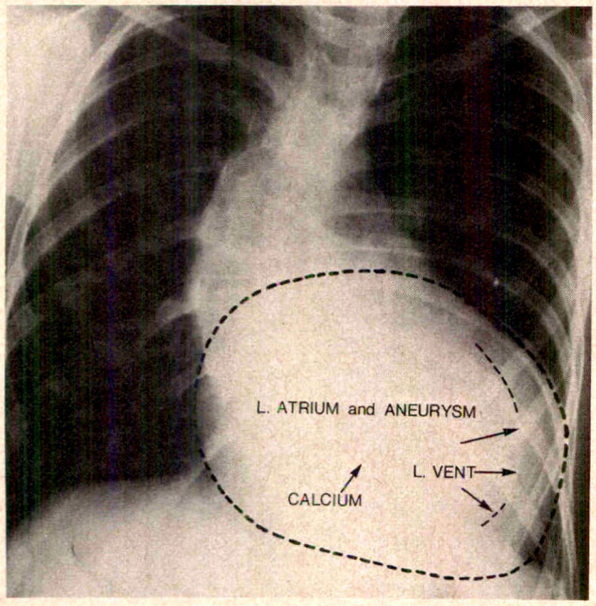
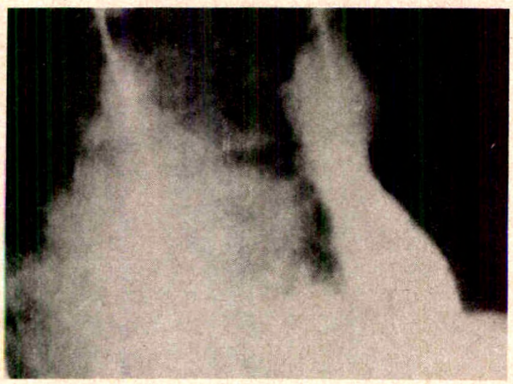


FIGURE 1. Posteroanterior chest roentgenogram. Moderate scoliosis is noted. Most of the cardiac shadow is made up by the enlarged left atrium and the large left atrial aneurysm **(outer dotted line).** The **single arrow** points to the small inner calcification. The **inside curvilinear dotted line (triple arrows)** indicates the site of the bottom of the left ventricle which was later confirmed by angiocardiography and surgery. L. = left; VENT = ventricle.

Physical examination on admission revealed a thin adolescent girl with a blood pressure of 90/65 mm Hg. Apical pulse rate was 70/min. The chest was clear to percussion and ausculation. Cardiac examination revealed a regular rhythm with no thrill or abnormal impulse. The first heart sound was soft and the second sound was widely split with the pulmonic component louder than the aortic. A grade 3/6 harsh holosystolic murmur was audible at the apex and radiated into the left axilla. A grade 2/6 early diastolic murmur of low intensity also was heard at the apex. No clicks or extracardiac sounds were audible. There was severe dextroscoliosis of the thoracic spine. Since the possibility of a cardiac tumor could not be excluded, a fourth cardiac catheterization with cineangiocardiography was performed. The findings confirmed the presence of mild mitral insufficiency and demonstrated what was believed to be an aneurysm or tumor of the left ventricle (Fig. 2). The cardiac catheterization findings are summarized in Table I.

Operation was recommended. A median sternotomy was performed, and upon opening the pericardium, an 8 by 12 cm saccular aneurysm of the left atrium was found (Fig. 3). Under cardiopulmonary bypass, the thin-walled aneurysm was opened. No thrombi were present. The atrial appendage was normal and the mitral valve leaflets were slightly thickened. The aneurysm was resected and a 0.5 by 4 cm spicule of calcium arising from the endocardium of the posterior wall of the atrium was debrided. The patient had an uneventful postoperative course. No medications were prescribed on discharge.



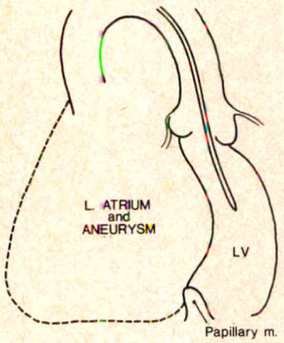
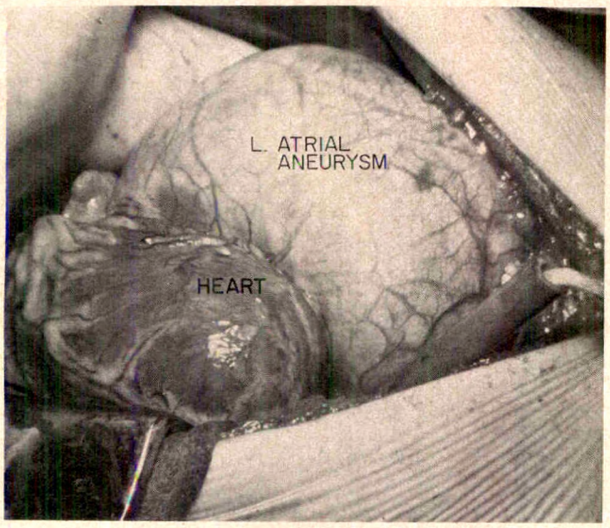


FIGURE 2. Left ventricular angiocardiogram and drawing. The root of the aorta and the left ventricle, visualized by retrograde introduction of the catheter and injection of contrast material, are well delineated. This frame is from the lateral series and clearly shows a very large structure filled with contrast medium that lies directly behind the left ventricle, indenting the ventricular septum. This turned out to be the left atrium and a large left atrial aneurysm. L. = left; LV = left ventricle; m. = muscle.



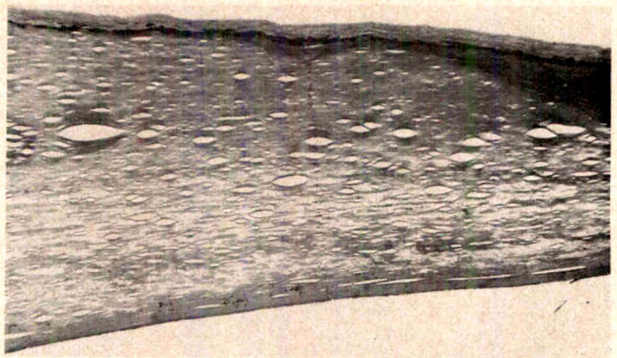


FIGURE 3 (left). Photograph of the heart and left atrial aneurysm showing their relation in situ at the time of surgical exploration. L. = left.

FIGURE 4 (above). Photomicrograph of a section of the wall of the left atrial aneurysm demonstrating the sparse, hypertrophied myocardial fibers and the thick epicardium. (Hematoxylin-eosin × 110, reduced by 50 percent.)

TABLE I

Cardiac Catheterization Data

	Age 1 Year	Age 2 Years	Age 10 Years	Age 13 Years
	Pressures (mm Hg)			
Left ventricle	NR	92/6	96/11–14	91/13
Ascending aorta	86/54	NR	84/60	85/52 (66)
Pulmonary wedge	NR	16/14	(17)	NR
Pulmonary artery	36/16	33/13	36/20 (22)	25/15
Right ventricle	46/0	37/1	28/1–5	28/7
Right atrium	9–12/3	8/4–12/9	*a* 5; (4) *v* 4	*a* 6; (3.5) *v* 4
Cardiac index (liters/min per m²)	NR	1.8	3.46	4.5

Figures in parentheses indicate mean pressures.
a = *a* wave; NR = not recorded; *v* = *v* wave.

Pathologic examination of the specimen revealed a 5 by 7 cm saccular structure about 1 mm thick. The atrial wall fibers were attenuated with thick fibrous epicardium and hypertrophy of the sparse myocardial fibers (Fig. 4).

In the 6 months since operation, the patient has remained asymptomatic with no episodes of arrhythmia. Serial roentgenograms have shown decreasing cardiomegaly and electrocardiograms show no evidence of recurrence of the arrhythmia.

Discussion

There are several previous reports[1–5,20] of left atrial aneurysm in patients with acquired valvular or myocardial disease. The presence of myocardial disease or chronically increased left atrial pressure, as seen in severe mitral stenosis secondary to rheumatic heart disease,[3] can predispose to development of an aneurysm. The appearance of left atrial aneurysm in early childhood in the absence of any recognized predisposing causes such as congenital heart disease, acquired inflammatory changes or other pathologic processes in the myocardium indicates a congenital origin.

Clinical findings: The clinical data in the six recorded cases (including that reported here) of congenital left atrial aneurysm are summarized in Table II. There were five children (aged 2 to 13 years) and one adult (aged 64 years). Roentgenographic evidence of cardiomegaly or a mediastinal mass was present in each case, and arrhythmia was observed at some time during the course of the disease in five. The origin of the arrhythmia is not known. It may be caused by tension on the conduction system from the enlarged atrial muscle mass, a circus movement phenomenon or a congenital defect in the conduction tissues.[7]

A systolic murmur was present in five cases, the location being apical in four[7,8,10] and not indicated in the one.[6] Two of these patients also had diastolic murmurs[10] suggesting real or relative mitral stenosis; one patient had no cardiac murmur.[9] Lack of angio-

TABLE II

Salient Features in Six Reported Cases of Left Atrial Aneurysm

Author	Age (yr) & Sex	Presenting Symptom or Sign	Chest X-Ray Findings	Angiography	Murmur	Arrhythmia on ECG	Preoperative Diagnosis	Operative Findings	Course
Semans and Taussig[10]	5F	Dyspnea, palpitations	Cardiomegaly	Not performed	Apical systolic, diastolic	Tachycardia (245/min)	No operation	Autopsy: LAA 6 × 10 cm, thrombus	Died 48 hr after admission
Pitts and Potts[9]	2M	Cough, tachycardia	Anterior mediastinal mass	Not performed	None	Atrial tachycardia	Tumor	LAA 6 × 10 cm, thrombus	No symptoms, normal ECG
Herbert et al.[6]	9M	Abdominal pain, syncope, cyanosis	Posterior mediastinal mass	Not performed	Systolic	Normal	Neurofibroma	LAA 5 × 5 cm	Symptoms slowly resolved, normal ECG, X-ray
Parker et al.[8]	64F	Paroxsymal arrhythmia, abnormal X-ray	Cardiomegaly	Dilatation of LA App, no MI	Apical systolic	Atrial flutter	LA App A	LAA, thrombus	No arrhythmia
Macleod et al.[7]	10F	Paroxysmal arrhythmia, murmur	Cardiomegaly	Cardiac tumor, trivial MI	Apical systolic	Normal, but SVT during angiography	Tumor	LAA 6 × 8 cm, no thrombus	No symptoms, normal ECG
Present authors	13F	Syncope, SVT	Cardiomegaly	Cardiac tumor Vent A, mild MI	Apical systolic, diastolic	SVT	Tumor or Vent A	LAA 8 × 12 cm, no thrombus	No symptoms, no arrhythmia, normal ECG

ECG = electrocardiogram; LAA = left atrial wall aneurysm; LA App = left atrial appendage; LA App A = left atrial appendage aneurysm; MI = mitral insufficiency; SVT = supraventricular tachycardia; Vent A = ventricular aneurysm; X-ray = chest roentgenogram.

cardiographic evidence of significant mitral insufficiency suggests that aneurysms are probably not secondary to malfunction of the mitral valve.[7,8]

The preoperative diagnosis was cardiac or mediastinal tumor in four of five cases.[6,7,9] One patient had a preoperative diagnosis of left atrial appendage aneurysm,[21] but at operation a left atrial aneurysm was found.[8] Semans and Taussig[10] described a patient who was not operated upon and subsequently died. All five patients treated by resection of the aneurysm recovered from operation and had no further episodes of arrhythmia.

Differential diagnosis: Although children with congenital mitral insufficiency may present features similar to those of left atrial aneurysm, there are some subtle differences. Supraventricular tachycardia with congenital mitral insufficiency is not common. In 33 reported cases of congenital mitral insufficiency,[22–24] the electrocardiogram demonstrated supraventricular tachycardia in only 3. Thus the presence of supraventricular tachycardia and the murmur of mitral insufficiency should lead one to suspect the possibility of left atrial aneurysm. In addition, the degree of enlargement of the cardiac silhouette is usually more striking in the patient with an aneurysm.

Intracardiac tumors, particularly left atrial myxomas, present commonly with cardiomegaly, arrhythmia and a cardiac murmur.[25–31] In 46 cases of cardiac tumors in children,[25,29,30,32,33] 81 percent of the patients had an abnormal cardiac silhouette and 40 percent had cardiomegaly. Cardiac calcifications were noted in 16 percent. There were eight instances of arrhythmia (18 percent): One patient had atrioventricular block,[29] one had nodal extrasystoles,[32] two had ventricular tachyarrhythmias,[30] two had supraventricular tachycardia,[25,30] and in two the type was not described.[33] A systolic murmur, usually apical, was present in 24 of the 46 cases (52 percent). Nineteen patients (41 percent) had both systolic and diastolic murmurs. Systemic embolization, a common presenting sign of cardiac tumor, was documented in 19 (41 percent) patients.

The type of arrhythmia may prove helpful in distinguishing left atrial aneurysm from cardiac tumor. It seems that supraventricular arrhythmias are more often associated with left atrial aneurysm, and ventricular arrhythmias are more often associated with ventricular tumors.

Angiocardiography is the most accurate means of distinguishing left atrial aneurysms from isolated congenital mitral insufficiency or cardiac tumor. Even with these studies, the diagnosis in some instances can be established only by operation.

Complications and management: Left atrial aneurysm is a potentially lethal disease even in the asymptomatic patient. The threat of embolization is always present and, although no instance of embolization has been recorded, the presence of thrombi in two patients indicates that this is a potential hazard. Serious arrhythmias do occur in most patients with this condition and are potentially fatal. Spontaneous rupture of the left atrium has not been reported, but it seems reasonable to assume that a huge atrial aneurysm is vulnerable to either spontaneous or traumatic rupture.

Operative excision, even in the asymptomatic patient, is the treatment of choice. Cardiopulmonary bypass is essential for the excision of left atrial aneurysm since it involves a major portion of the atrial chamber and mural thrombi may be present. This is in contrast to treatment of appendage aneurysms which can be amputated without use of circulatory support. The risk of operation is low, and the probability of eliminating future embolic episodes and arrhythmas is good.

Addendum

Eleven months after operation, the patient experienced two episodes of tachycardia highly suggestive of paroxysmal atrial tachycardia without electrocardiographic documentation. Repeat heart catheterization and angiography demonstrated mild mitral stenosis and mild mitral insufficiency. The patient was discharged without medication and continues to do well.

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Acute Dissecting Aortic Aneurysm Resulting from Retrograde Brachial Arterial Catheterization

Successful Operative Intervention

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A case of type I aortic dissection occurring as a complication of retrograde catheterization of the right brachial artery is described. The problem was immediately identified and, after appropriate studies were performed, operative intervention was successfully carried out. Although this lesion is an extremely rare complication of the catheterization procedure, the possibility of its occurrence must be kept in mind. Prompt recognition, accurate diagnostic evaluation and immediate operation can result in a successful outcome.

Dissecting aneurysm of the aorta resulting from retrograde cardiac catheterization is a rare complication. Several prospective and retrospective studies[1–8] have documented the incidence of major and minor complications of catheterization and angiographic procedures. Although localized aortic dissection and subintimal injections of contrast material have been reported, little mention has been made of dissections of surgical significance. The following case is presented to emphasize this potential hazard and the importance of its immediate recognition and prompt treatment.

Case Report

A 55 year old white man was admitted to the University of Virginia Hospital on November 1, 1970 for evaluation of recurrent episodes of chest pain and syncope. In the year before admission his symptoms gradually increased in frequency; an evaluation by his local physician revealed a cardiac murmur suggestive of aortic stenosis.

Physical examination revealed a well developed, well nourished white man. Blood pressure was 160/100 mm Hg, pulse 80/min and regular. Examination of the heart revealed a thrill at the upper right sternal border and a grade 4/6 systolic murmur in the aortic area. Peripheral pulses were strong and equal bilaterally; no bruits were present.

An electrocardiogram revealed sinus tachycardia and evidence of left ventricular hypertrophy. A chest roentgenogram was noncontributory (Fig. 1A), but fluoroscopic examination revealed calcification in the area of the aortic valve.

The initial clinical diagnosis was calcific aortic stenosis and possible coronary artery disease. On November 4, 1970 the right brachial artery was catheterized with a no. 7F National Institutes of Health catheter. As the catheter was advanced into the area of the innominate artery, the vessel was noted to be extremely tortuous. In an attempt to delineate the course of the artery before advancing the catheter, small amounts of contrast material were injected and appeared within the wall of the subclavian artery. Almost immediately, the patient complained of severe chest pain requiring administration of narcotic agents. Because further fluoroscopic observation suggested widening of the superior mediastinum, the procedure was terminated. Although pain continued, the patient's vital signs remained stable. A chest roentgenogram confirmed widening of the mediastinum and suggested a double shadow of the aortic knob. The pain persisted and radiated to the back. Four hours later, hypotension developed and a repeat chest roentgenogram showed further widening of the mediastinum (Fig. 1B). Aortic dissection with developing cardiac tamponade was suspected, and a retrograde femoral aortogram was

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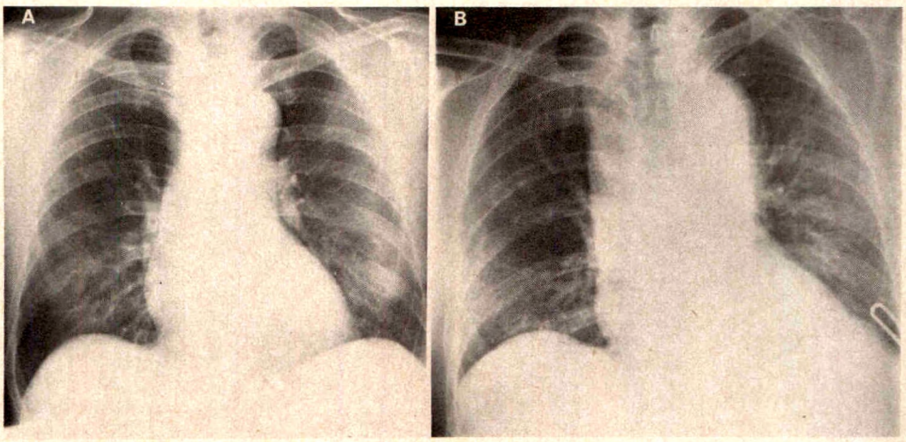

FIGURE 1. Roentgenograms. **A,** on admission. **B,** 4 hours after brachial arterial catheterization demonstrating marked mediastinal widening and double density at the aortic knob.

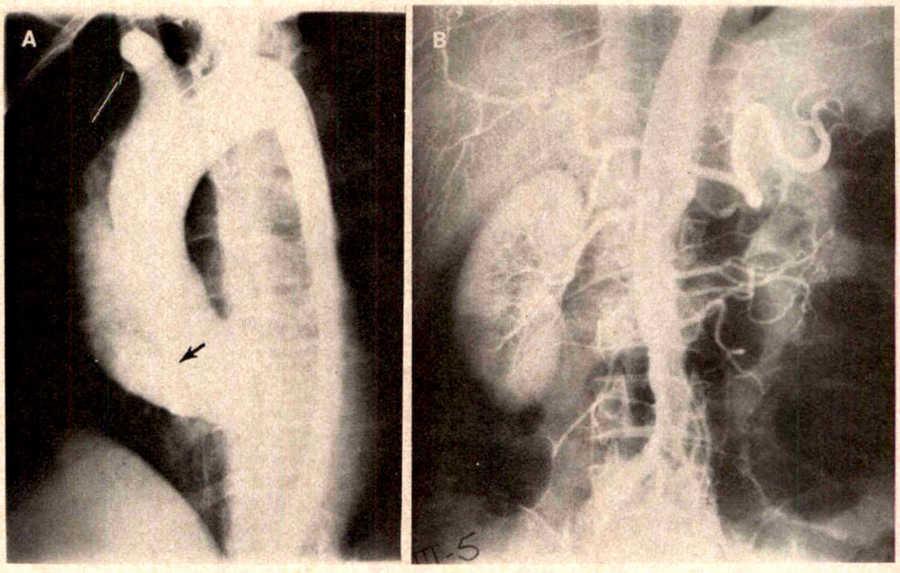

FIGURE 2. Femoral aortograms. **A,** indicating an intimal tear in the ascending aorta **(solid black arrow)** and extravasation of contrast material in the innominate artery at the level of injury **(white-bordered arrow). B,** abdominal phase, demonstrating extension of the dissection to the common iliac vessels.

immediately performed. This revealed a dissection of the aorta beginning at the aortic root and extending throughout the length of the thoracic and abdominal aorta (Fig. 2). The presence of intraluminal extravasation and dissection into the innominate artery suggested that the dissection originated in this area. Because of continued hypotension and paradoxical pulse, immediate operation was performed.

Exploration through a median sternotomy revealed blood in the pericardial sac and tamponade. After appropriate cannulation, cardiopulmonary bypass was begun, and the ascending aorta was cross-clamped just proximal to the innominate artery. The aorta was opened and transected at the level of the intimal tear. The distal end of the aorta was oversewn with a running suture, obliterating the false lumen. The aortic valve was congenitally deformed and heavily calcified, although only mildly stenotic. The dissection had detached the right coronary cusp, and it was believed that repair would not result in a satisfactorily functioning valve. A no. 13 Starr-Edwards aortic prosthesis was inserted and aortic continuity restored by interposition of a short segment of woven Teflon® graft. Perfusion of the left coronary artery had been maintained throughout the procedure, and cardiopulmonary bypass was discontinued

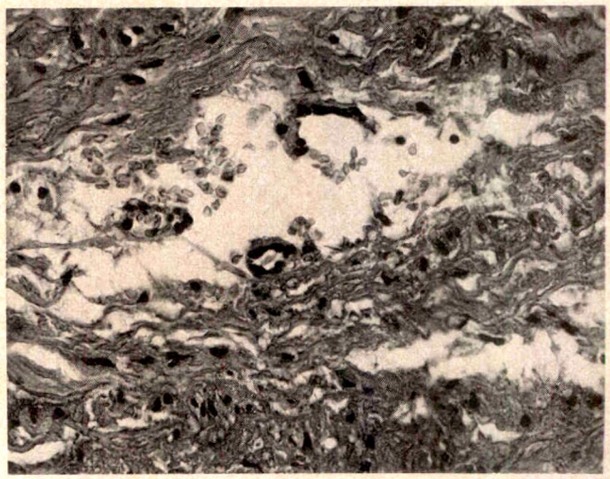

FIGURE 3. Photomicrograph of aortic media showing cystic medial degeneration with hemorrhage from ruptured vasa vasorum. The basophilic ground substance, easily seen in the slide, is not evident in the black and white photograph. Hematoxylin-eosin ×520, reduced by 26 percent.

without difficulty. In the immediate postoperative period, the patient's course was complicated by an episode of pericardial tamponade that required opening the lower end of the incision and evacuation of collected blood. The patient's condition then stabilized, and the remainder of the postoperative course was uneventful. He was discharged on the 11th postoperative day in satisfactory condition and has had no recurrent episodes of syncope or chest pain since discharge. On his last visit, 18 months postoperatively, he was doing well.

Pathologic examination of the resected specimen of aorta revealed atherosclerosis and focal mucoid degeneration in the media (Fig. 3). Examination of the aortic valve revealed thickening and calcification.

Discussion

In a cooperative, prospective study involving 12,367 catheterization procedures, there was a 3.6 percent prevalence of major complications.[1] Of the arterial complications, the most common was thrombosis. Only seven cases of dissection occurred.[2] Three local coronary arterial dissections resulted in two myocardial infarctions and one death[3]; of four localized dissections of the intrathoracic great vessels, only one required operation for obstruction. A report of 53 complications of left heart catheterization over a 36 month period noted 12 episodes of local peripheral arterial dissection of which 3 required repair,[8] two for occlusion of a peripheral vessel. Lang[4] reported a survey of 11,402 percutaneous retrograde angiographic procedures revealing a major complication rate of 0.7 percent. Local dissection is mentioned only as a causative factor in peripheral arterial obstruction. As a minor complication, intramural or subintimal injection of contrast medium was frequently reported, having occurred in 136 instances without sequelae. In several other large series reviewed, no mention is made of dissection as a major complication.[5–7]

In 1972, Cooley et al.[9] reported successful treatment of an ascending aortic dissection that occurred during coronary angiography. In their case, catheterization of the left brachial artery was followed by pain and resistance at the level of the innominate artery. After removal of the catheter, coronary angiograms obtained by the percutaneous femoral approach, disclosed severe coronary artery disease and the patient was referred for operative intervention. At operation, a dissection of the ascending aorta was found and repaired with a Dacron® patch. Saphenous vein bypass grafts from the prosthesis to the right coronary artery and the left anterior descending vessel were also performed. The patient had an uneventful recovery.

The mechanism of spontaneous aortic dissection is not established but is dependent on preexisting degenerative disease in the aortic media. The event is probably started by hemorrhage into an area of medial necrosis with extension of the dissection developing in part by expansion of the hematoma. Alternatively, the hematoma may rupture through the intima and allow the entrance of blood under pressure to extend the dissection. Experimental studies have demonstrated that separation of the media in a normal aorta requires such high injection pressures that it can be concluded dissection cannot occur in the absence of medial disease.[10] Dissection has been produced experimentally in dogs with a normal aorta, but the clinical appearance and course were not similar to those observed in man.[11]

Since subintimal injections frequently occur in catheterization procedures without significant complications or dissection, it seems reasonable to assume that degenerative medial disease is a prerequisite for dissection. This was the situation in the case reported here since pathologic examination revealed focal mucoid degeneration, a finding typically seen in cystic medial necrosis. Presumably the process is initiated by subintimal injection of contrast material. If a vessel diseased by degenerative changes is involved, this may be enough to start the dissection. The dissection may be self-limiting or, as demonstrated in our case, an intimal tear may occur and result in progressive and complete aortic dissection.

Clinical implications: As an increasing number of patients with advanced atherosclerosis undergo catheterization for evaluation of coronary artery disease, the existence of diseased and tortuous peripheral vessels must be appreciated. If a difficult catheterization occurs, extreme care must be taken in manipulation of the catheters and careful hand injections of small volumes of contrast material utilized to assess the situation. In spite of adherence to the principles of careful technique, aortic dissection can occur. It is imperative that the problem be recognized immediately and that appropriate diagnostic studies be obtained. Typical signs and symptoms of a dissecting aneurysm may be observed. Serial chest roentgenograms should reveal the appearance of a double shadow in the area of the aortic knob or progressive mediastinal widening. Once the diagnosis is suspected, angiograms must be obtained for confirmation. Surgical intervention should be considered if the appropriate indications are present. These include pericardial tamponade, severe aortic insufficiency, progressive pain, persistant hypotension or major peripheral vascular obstruction. Prompt and aggressive surgical intervention can be effective and life-saving. The case we have described and that reported by Cooley et al.[9] demonstrate that simultaneous correction of a coexisting problem such as valve replacement or coronary artery bypass grafting can be performed successfully.

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Successful Total Repair of Interrupted Aortic Arch Associated With Ventricular Septal Defect and Large Patent Ductus Arteriosus

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Successful total repair in one procedure was performed in a case of interrupted aortic arch associated with ventricular septal defect and large patent ductus arteriosus. The surgical technique is described and results of postoperative angiography are analyzed. The literature and results of previous surgical attempts at correction are reviewed.

The complex malformation of interrupted aortic arch associated with ventricular septal defect and large patent ductus arteriosus feeding the descending aorta is a rare condition that has seldom been successfully repaired.[1–3] A case, in a young 8 year old boy, presented an opportunity to review the literature on this defect and evaluate recent progress in treatment.

Case Report

A cardiac lesion was detected in a boy soon after birth after a full-term, normal pregnancy and delivery. The weight at birth was only 2.5 kg, and growth was slow and marked by repeated chest infections. Later the child experienced shortness of breath while playing or running, and was constantly underweight in relation to his age and size. In 1968 at age 5 years he was admitted to the hospital for treatment of a respiratory tract infection.

On examination the child was markedly underweight and was in considerable respiratory distress. There was no cyanosis or clubbing. The blood pressure in the right arm was 160/110 mm Hg; all pulses were equally palpable. Examination of the lungs revealed consolidation of the left lower lobe and crepitation in both lungs. A fairly prominent central sternal bulge was present, and cardiac examination showed signs of gross cardiomegaly with left and right ventricular hypertrophy. There was a systolic thrill over the precordium; a grade 5/6 pansystolic murmur was maximal at the lower left sternal border, and a grade 2/4 mid-diastolic rumbling murmur at the apex. The second heart sound was not split, but it was markedly accentuated. The electrocardiogram showed biventricular hypertrophy and the chest X-ray film marked cardiomegaly, considerable pulmonary plethora and left lower lobe consolidation. The clinical diagnosis was ventricular septal defect with a large left to right shunt and marked pulmonary hypertension. The increased blood pressure was attributed to peripheral vasoconstriction. The pneumonia responded to medical treatment.

Cardiac catheterization: One year later data obtained at cardiac catheterization revealed a ventricular septal defect with a left to right shunt of 44 percent and a right to left shunt of 19 percent. The pressure in the right ventricle was equal to that in the descending aorta but only half that in the left ventricle. The pulmonary vascular resistance was normal, but angiograms showed an interruption of the aortic arch (Fig. 1) between the left carotid and left subclavian arteries (Celoria and Patton[4] type B) (Fig. 2). A patent ductus arteriosus was connected to the descending aorta, and there was a small bidirectional shunt through the ductus. The aortogram showed large,

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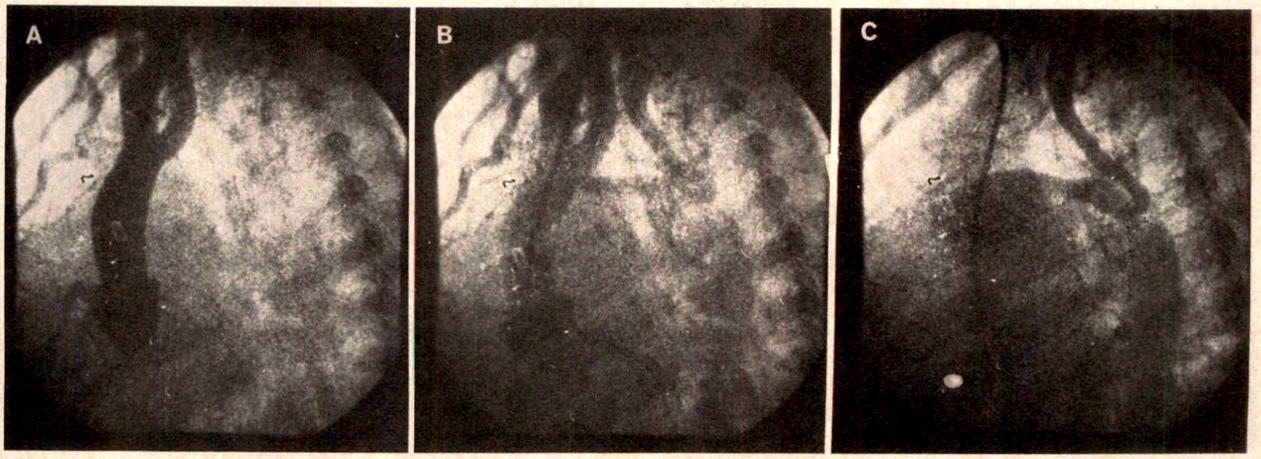

FIGURE 1. Preoperative aortic angiograms. **A,** early films showing the ascending aorta, the aortic interruption, and some collateral vessels. **B,** later film showing ascending aorta, collateral vessels and filling of the left subclavian artery by collaterals. **C,** late film showing collateral filling of the left subclavian and descending thoracic aorta, and diastolic filling of a large pulmonary artery by the ductus.

tortuous internal mammary arteries feeding the left subclavian artery through collateral vessels. There was delayed filling of the aorta through these connections. Contrast material refluxed into the patent ductus during diastole, and during systole the flow appeared to be from the ductus to the descending aorta (Fig. 1C).

Subsequently, the child was readmitted twice for upper respiratory tract infections and it was noticed that signs of congestive cardiac failure had developed and the blood pressure had increased. The pressure in the right arm was now 200/100 and in the left arm 100/65 mm Hg. There was no radial femoral pulse delay. The patient was treated with digitalis and diuretic agents and underwent surgical correction.

Surgical repair: At operation a left posterolateral thoracotomy was performed to divide the ductus arteriosus and to make an end to end anastomosis between the descending aorta and a 1/2 inch Dacron® vascular graft. A median sternotomy was performed (Fig. 3). The patient was placed on total cardiopulmonary bypass, and the ventricular septal defect was closed with a 1 1/2 by 2 1/2 cm Teflon® felt patch. During rewarming the Dacron vascular graft was pulled into the anterior mediastinum, through a window in the pericardium above the left phrenic nerve, and was anastomosed end to side to the proximal part of the ascending aorta (Fig. 3). Bypass was discontinued. The patient was routinely ventilated for the first 24 hours after operation.

The child made an uneventful recovery apart from severe systemic hypertension in the early postoperative period, with a systolic blood pressure increasing at times to 260 mm Hg. This condition was treated medically and was

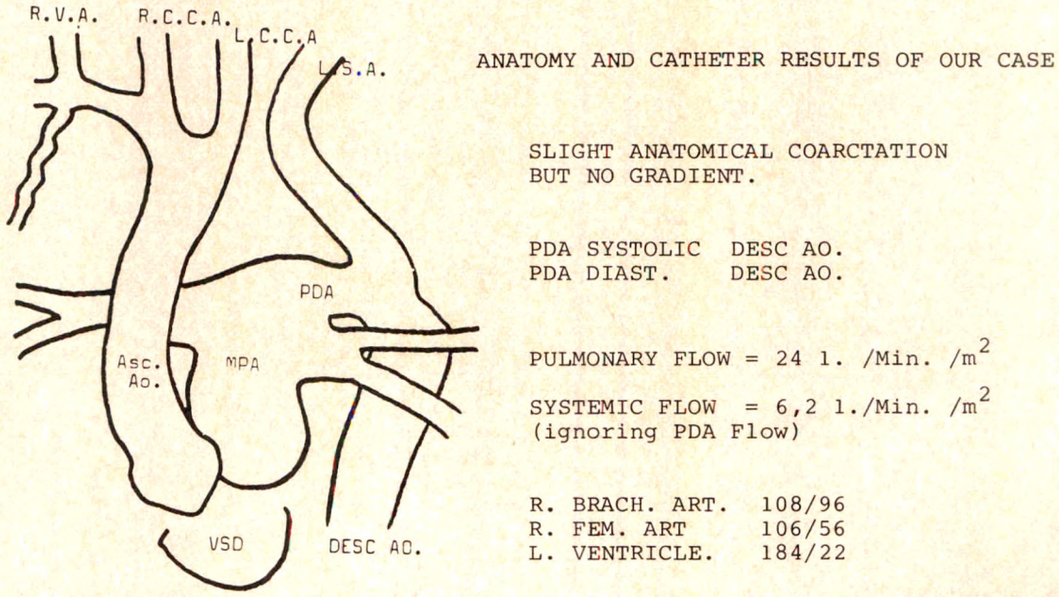

FIGURE 2. Diagram showing the interrupted arch, the ductus and ventricular septal defect. Asc. Ao. = ascending aorta; BRACH. ART. = brachial artery; CCA = common carotid artery; DESC. AO. = descending aorta; DIAST. = diastolic; FEM. ART = femoral artery; L. = left; MPA = main pulmonary artery; PDA = patent ductus arteriosus; R. = right; V.A. = vertrebral artery; S.A. = subclavian artery; VSD = ventricular septal defect.

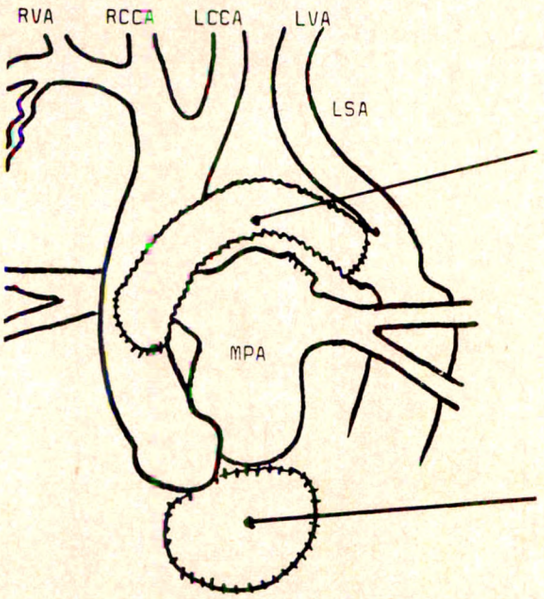

FIGURE 3. Diagram of the surgical repair. Abbreviations as in Figure 2.

abolished completely 12 days postoperatively. When the patient was discharged, the blood pressure was 140 to 150/85 mm Hg in the right arm and the cardiovascular status was normal. The femoral and left brachial pulses were all present but weaker than the right brachial pulse.

Before the patient's discharge an aortogram was performed by way of the right brachial artery; the film showed good, rapid filling of the graft, with backflow from the graft into the left subclavian artery and the major collateral vessels (Fig. 4). No significant gradient could be found, and it was postulated that the relative weakness of the femoral pulses resulted from the damping effect of the long, rigid Dacron graft.

Discussion

Fewer than 200 cases of interrupted aortic arch have been reported, fewer than 20 patients have been operated on successfully, and only three or four total corrections of the interrupted arch and associated anomalies have been performed (Table I).

Despite anatomic similarities with coarctation of the aorta, extension of interruption and associated lesions make this syndrome one of the most rapidly lethal forms of congenital malformation; 95 percent of infants affected die in the first year of life and most of them in the first days or weeks.[5] Van Praagh,[6] in a study of 174 consecutive autopsies of neonates, reported that this syndrome was the commonest cause of death (31 percent) from all congenital heart diseases in the first month of life.

Natural survival beyond infancy is related to the extent of the obstruction to blood flow through a segment of aorta and the associated anomalies. Our patient fulfilled two of the three prerequisites for successful tubular grafting outlined by McNamara and Rosenberg [2]—aortographic evidence of adequate collateral vessels and a significant systolic pressure gradient between proximal and distal aortic segments.

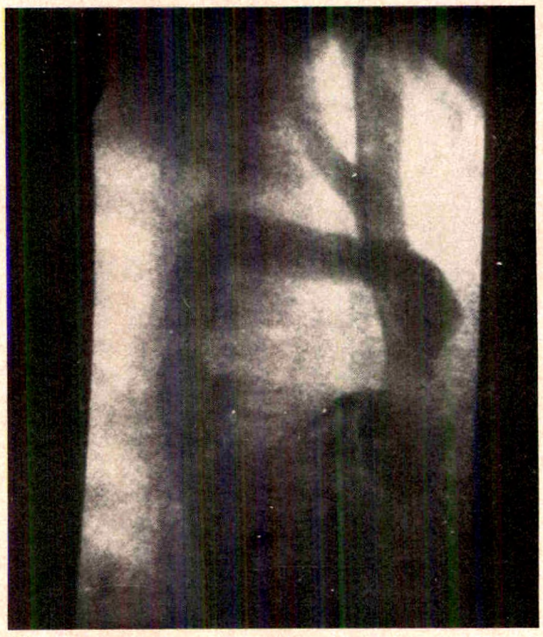

FIGURE 4. Postoperative aortic angiogram. Injection just above aortic valve showing the ascending aorta, Dacron graft and descending aorta.

The various forms of the syndrome have been classified by several workers, in particular Celoria and Patton,[4] who divided interruptions of the aortic arch according to the site of interruption (Fig. 5). In type A, complete interruption of the aorta occurs distal to the left subclavian artery. In type B, the defect is localized between the left carotid and left subclavian arteries, and in type C it is proximal to the left carot-

TABLE I

Reported Cases of Surgical Treatment of Interrupted Aortic Arch and Associated Lesions

Authors	Year	Age	Sex	Type	Surgical Procedure & Complications
A. Successful Surgical Partial Correction or Palliation					
Mustard et al.[8]	1957	7 1/2 mo	F	A	Aortic arch mobilized; anastomosis of aortic arch and descending aorta; PDA ligated successfully. VSD closure 3 5/12 yr; A–V block when coronary sinus sucker inserted. Death from A–V block 4 1/12 yr
Ruiz Villalobos et al.[9]	1961	14 yr	M	A	PDA divided; left subclavian graft-descending aorta anastomosis
Blake et al.[10]	1962	20 mo	M	B	Dacron graft of ascending aorta; PDA divided
Hairston et al.[11]	1967	11 mo	F	B	Bilateral PA branch banding; transverse bilateral thoracotomy
	1967	6 yr	M	A	Corrected TGAs with Teflon graft from ascending to descending aorta with division of PDA
Sissman et al.[3]	1968	2 mo	M	A	Ductus closed spontaneously; MPA banding. Almost asymptomatic at 5 yr
	1969	15 yr	M	A	Left subclavian-descending aorta graft and PDA division; subsequent aorta-PA septal defect repair.
Sirak et al.[12]	1968	1 mo	M	A	L common carotid to left subclavian artery anastomosis end-to-end with descending aorta; PDA divided; MPA banded. Died 5 wk postop with VSD small.
Asano et al.[13]	1968	21 yr	—	A	Distal to left subclavian artery. VSD and PDA. Prosthetic graft from ascending to descending aorta
Taniya et al.[14]	1968	22 yr	—	A	Distal to left subclavian artery. Unknown. Prosthetic graft from ascending to descending aorta
Miki et al.[15]	1968	8 yr	—	A	Proximal to left subclavian artery. VSD and PDA direct anastomosis; VSD repaired later.
Tyson[16]	1969	12 days	F	A	MPA banded; PDA resected; end-to-end anastomosis clavian artery-descending aorta
Van Praagh[6]	1969	11 days	M	B	Teflon graft MPA-descending aorta; LPA banding; RPA banding at 3 mo
Murphy et al.[17]	1970	3 mo	M	A	PDA and VSD; ligation of PDA; innominate artery to descending aorta anastomosis; banding of pulmonary artery.
	1970	10 days	M	A	PDA, VSD and TGAs. Ligation of PDA; innominate artery to descending aorta anastomosis; banding of pulmonary artery.
B. Total Surgical Correction of Interrupted Aortic Arch Without any Associated Lesions					
Pillsbury et al.[18]	1964	16 yr	F	C	Between innominate and left common carotid arteries. None. Prosthetic graft from ascending to descending aorta
Zetterqvist et al.[19]	1967	8 yr	—	B	Proximal to left subclavian artery. None. Direct anastomosis
Asano et al.[20]	1967	12 yr	—	B	Proximal to left subclavian artery. None. Prosthetic graft from ascending to descending aorta
C. Total Surgical Correction of the Interrupted Aortic Arch and Associated Lesions in One Procedure					
Merrill et al.[21]	1957	3 1/2 yr.	F	B	PDA divided; anastomosis to side of left subclavian artery; VSD's (2) closed successfully, 7/12/61
Barratt-Boyes et al.[1]	1970	8 days	F	A	PDA, VSD and total anomalous pulmonary venous connection. Graft from ascending to descending aorta, closure of VSD and closure of ASD with drainage of pulmonary veins and coronary sinus in the left atrium
Present case	1973	8 yr	M	B	PDA and VSD; graft from ascending to descending aorta; division of PDA and closure of VSD

ASD = atrial septal defect; A–V = atrioventricular; LPA = left pulmonary artery; MPA = main pulmonary artery; PA = pulmonary artery; PDA = patent ductus arteriosus; RPA = right pulmonary artery; TGAs = transposition of great arteries; VSD = ventricular septal defect.

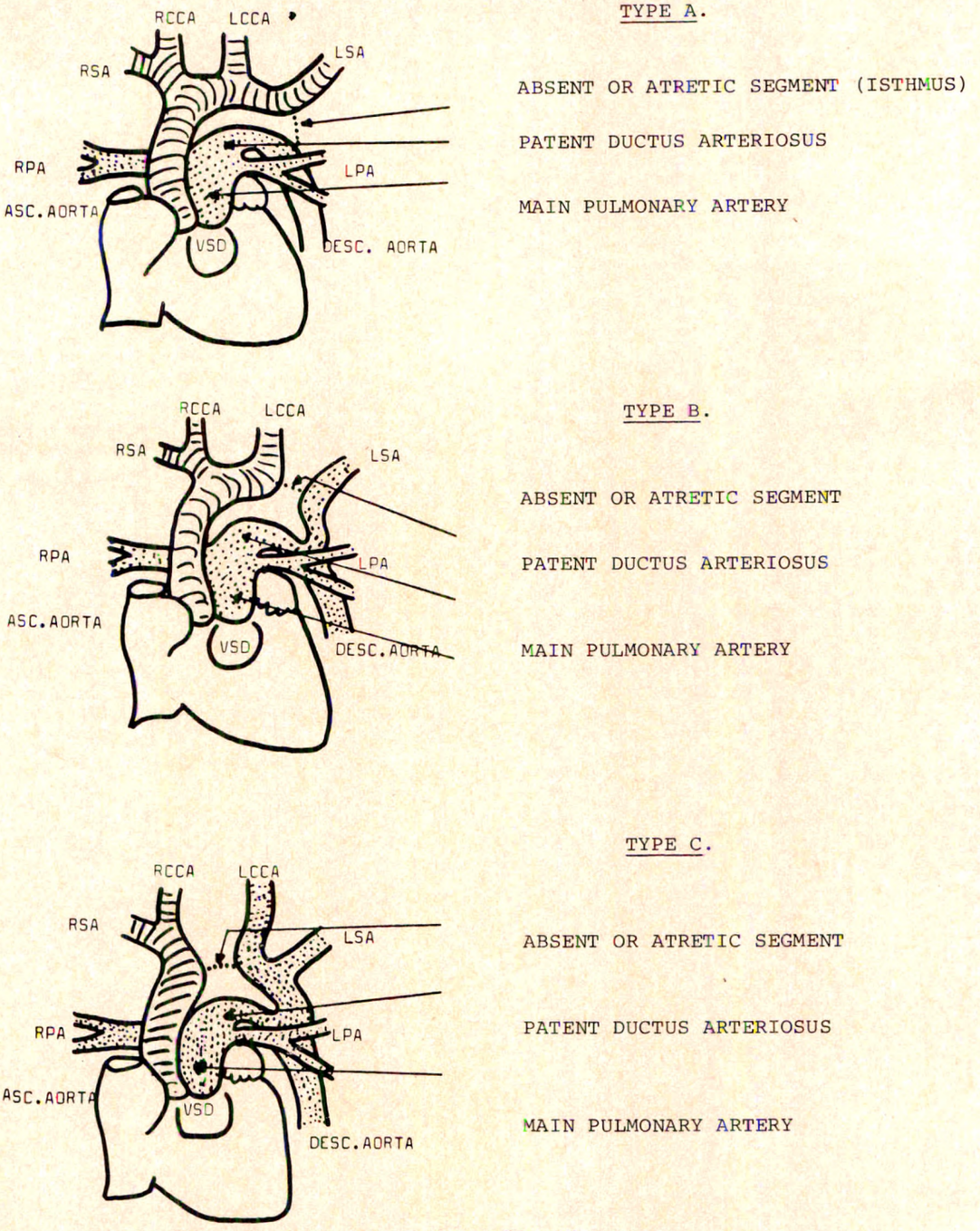

FIGURE 5. Diagrams illustrating the three types of interrupted aortic arch. PA = pulmonary artery.

id artery. Roberts et al.[7] reported prevalence rates of 44 percent for type A, 52 percent for type B and 4 percent for type C in their series. Multiple associated abnormalities were the rule, commonly ventricular septal defect and patent ductus arteriosus. Other defects included bicuspid aortic valve with subvalvular stenosis, multiple abnormalities of the great vessels arising from the arch, and complex intracardiac anomalies. The embryologic process leading to interrupted aortic arch differs from that resulting in coarctation of the aorta. The complex developmental changes in the embryo, which eventually result in the normal aortic arch, involve processes of reabsorption and growth of the primitive double arch. Interrupted aortic arch is due to hypoplasia of some of the elements constituting the arch.

The poor results of previous attempts at correction were related to the severity of the associated anomalies, the degree of disability of the child, and the use of surgical procedures that only partially corrected

the defects present (banding of the main or left and right pulmonary arteries, reestablishment of a large shunt between the main pulmonary artery and the descending aorta). However, with recent progress in surgery total corrections in one procedure may be performed successfully. Even in neonates the prognosis of interrupted aortic arch, which until recently was extremely poor, will be reversed because of new developments in neonatal resuscitation and the use of deep hypothermia with short periods of extracorporeal circulation.

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LETTERS TO THE EDITOR

HEART RATE IN ACUTE MYOCARDIAL INFARCTION

The article entitled "Deleterious Effects of Increased Heart Rate on Infarct Size in the Conscious Dog" by Shell and Sobel[1] presented data obtained in the fastidious manner one has come to expect from that laboratory. It is not my intention to discuss the problem of the extent to which creatine phosphokinase levels mirror actual changes in infarct size, but rather to consider the significance of their findings for the prehospital phase of the patient with acute myocardial infarction. I have, with one exception, no problem with what the authors stated but rather with what they didn't state.

The one exception is related to their reference to "routine administration of atropine to prevent ventricular arrhythmias . . .," as if this, in fact, might have been contemplated. No one that I am aware of, least of all the undersigned, has proposed such a *routine* use of atropine. It would, I believe, be foolish to do so. Nor do I see any rational basis for increasing the heart rate of the in-hospital infarct patient with bradycardia whose condition is stable and who does not exhibit ectopy, hypotension or signs of congestive failure.

On the other hand, the authors might wish to express their views about the relevance of their findings to the use of atropine when bradycardia is present in the first 30 minutes of acute myocardial infarction in light of the recent findings in the valuable study of Webb et al.[2] In that study, half of the patients observed in the first 30 minutes had heart rates of 60/min or less. Of those who had such bradyarrhythmia, four of five had a systolic pressure of 100 mm Hg or less, and every second patient had a systolic pressure of 80 mm Hg or less.

It seems self-evident that the maintenance of coronary perfusion pressure is a fundamental requirement of an ongoing circulation. If one adds to this the great likelihood that flow to the peri-infarcted myocardium (marginal area) will depend to a substantial extent on flow through collateral vessels, the maintenance of an adequate coronary perfusion pressure seems essential not only to the longevity of the patient but also to limitation of the ultimate size of the infarct.

In short, do the authors deduce from their data that an increase in bradycardic heart rates is undesirable in the presence of hypotension in the early phase of acute myocardial infarction? Or would they consider the use of atropine appropriate in such circumstances in view of the findings that atropine, when so used, almost uniformly elevates hypotensive levels of arterial pressure in addition to inducing an increase in heart rate?

Stanley J. Sarnoff, MD, FACC
Survival Technology, Inc.
Bethesda, Maryland

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REPLY

Dr. Sarnoff's interest in our work is most appreciated. In the study to which he refers, we demonstrated that "infarct size" can be determined objectively, antemortem, under controlled conditions in conscious dogs with coronary occlusion and that infarct size in this model is augmented when heart rate is accelerated by ventricular pacing or administration of isoproterenol or atropine. Our study was *not* directed toward the prehospital phase of acute myocardial infarction in man per se. However, as underscored by Dr. Sarnoff's own work and fundamental contributions, elucidation of phenomena with clinical implications often requires parallel experimental explorations under rigorously controlled conditions. We have recently shown that analysis of serial changes in serum creatine phosphokinase activity after experimental and spontaneous myocardial infarction provides an index of infarct size.[1,2] Further, it is becoming increasingly clear that infarct size is an important determinant of prognosis.[2,3] Under specific conditions in which atropine increases infarct size, such as those described in our investigation, administration of the agent is deleterious. Extension of these findings to the more complex clinical situation should not be undertaken lightly. In fact, our investigation was designed in part to develop a means for gathering objective information on the effect of atropine and other interventions on infarct size and, hence, prognosis under specified experimental and clinical conditions.

Available clinical evidence regarding the value of atropine early after infarction is equivocal. Bradycardia is common in patients with posterior acute myocardial infarction and is often associated with hypotension.[4] Atropine frequently reverses both. However, it is not clear that infarct size or mortality is adversely influenced by the transient bradycardia. It remains to be shown that vigorous treatment of bradycardia early after infarction will significantly improve survival.[5] Despite Dr. Sarnoff's explicit admonitions against the routine use of atropine, there has been a tendency among some to embrace this measure uncritically or overenthusiastically. In addition to the data in our study, other experimental results attest to deleterious effects of accelerated heart rate when the heart is ischemic. For example, the extent of myocardial injury detected electrocardiographically is increased.[5,6] Although ischemia or bradycardia alone increases temporal dispersion of refractoriness, acceleration of heart rate induced by atropine in the presence of ischemia accentuates the temporal dispersion of refractoriness associated with ischemia alone, thus facilitating reentrant dysrhythmias.[7] In addition, both the threshold for ventricular fibrillation and the occurrence of "malignant" ectopic activity in the ischemic heart are increased by atropine.[7]

In patients, injudicious doses of atropine may precipitate ventricular tachycardia.[4] Accordingly, it is particularly important to identify subsets of patients with acute myocardial infarction who may be benefited by treatment with atropine in the prehospital phase.

As pointed out by Dr. Sarnoff, bradycardia associated with acute myocardial infarction is often associated with hypotension. Presumably, under these circumstances infarct size would be increased as a function of the duration and severity of diastolic hypotension sufficient to compromise coronary flow. On the other hand, since myocardial oxygen requirements are undoubtedly reduced when heart rate is decreased, transient bradycardia may decrease the disparity between myocardial oxygen requirements and myocardial oxygen supply associated with a given coronary perfusion pressure. We concur that hypotension associated

with bradycardia and responsive to augmentation of heart rate with atropine should be corrected promptly by judicious administration of this agent to patients with acute myocardial infarction. However, administration of atropine to all patients with transient bradycardia associated with infarction would be justified only if it were established (1) that bradycardia was invariably responsible for hypotension responsive to the drug and sufficiently prolonged to jeopardize myocardium, or (2) that bradycardia consistently contributed to development of major dysrhythmias, a point not substantiated by recent experimental data.[8] We do not believe that either of these premises is justified on the basis of present information. Acceleration of heart rate induced by atropine augments infarct size when preexisting hypotension is absent, as shown in our report. Thus, in our view the use of atropine as a therapeutic modality generally applicable to patients with acute myocardial infarction in the prehospital phase, even those with transient bradycardia, is not presently justified and requires further exploration in carefully controlled studies.

Methods such as those described in our report should allow objective assessment of the effect of potentially therapeutic interventions on infarct size, an important determinant of prognosis in patients with acute myocardial infarction. The complex issues addressed in Dr. Sarnoff's letter can best be resolved by both clinical investigation and rigorous experimental assessment of the effect of alteration of heart rate on hemodynamics, dysrhythmias, infarct size and mortality.

William E. Shell, MD
Burton E. Sobel, MD
University of California, San Diego
Department of Medicine
La Jolla, California

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ACADEMIC VS. COMMUNITY SURGEONS

A recent editorial by Dr. Effler in this Journal[1] sharply criticized the academic segment of the surgical establishment and praised the high order of surgical practice in some community hospitals. Effler specifically mentioned my own community of Flint, Michigan, where a large number of saphenous vein bypass grafts have been performed with low mortality. As a practicing cardiac surgeon, I was pleased that our community had received this recognition.

On close examination, Effler was giving us a back-handed compliment: The academic surgeons are so bad that even the community surgeons look good. Effler proposed that an external auditor should evaluate the competency of each cardiac catheterization laboratory and each surgical team.

I am not sure whether this would help the academic surgical community, but I am quite certain that it would be detrimental to the cardiac surgical teams in the smaller centers that Effler seems to admire. What is clearly needed are more unbiased statistics, more carefully evaluated indications for surgery, and more critically examined results. I suspect we need more heretics and fewer evangelists in this field at the moment. Oneupmanship is practiced at the community level as in academic centers. I doubt that putting more uncritical reports in print from community hospitals would be of help to anyone. Unlike Effler, I would encourage the editors of our journals to be even more critical of statistical material and I implore our academic colleagues to be even more demanding of our surgical efforts in this field.

Lloyd H. Hudson, MD
McLaren General Hospital
Flint, Michigan

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REPLY

The purpose of my editorial was not to give anybody a compliment, but simply to state the facts as I see them. There is considerable opposition on the part of cardiologists to revascularization surgery in any form, and the dismal results that have been published in many of our academic centers are used constantly as ammunition against this current surgical trend.

Having been in this business for quite a while, I am convinced that the surgical treatment of coronary disease would be best handled by those who get the best results. After my tour of duty on the Coronary Committee of the I.C.D.H., I was impressed by the fact that many of our surgical leaders have no idea of what is going on in this business. Like Dr. Hudson, I am a firm believer in presenting the profession at large with "unbiased statistics and critically examined results." Each year we publish the Cleveland Clinic results, but these are usually cast aside as being unrepresentative of what can be accomplished in the United States. There are still a few people who should know better who believe the Cleveland Clinic Hospital is constructed with the tusks of large male elephants, and that we are able to accomplish things that cannot be accomplished on the outside. The point of my editorial was to state simply that this is not the fact and that many community hospitals are achieving results that are comparable to ours. . . . It was not my intent to suggest that academic surgeons are awful and that community surgeons look good as a result. I did state quite frankly that the aura of the academic center may not be entirely justified on the basis of its surgical results, and this I believe to be true.

Donald B. Effler, MD
Cleveland Clinic
Cleveland, Ohio

REVIEWS IN CARDIOLOGY*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ADAMS-STOKES SYNDROME

Surdocardiac and related syndromes in children. Jervell A. **Adv Intern Med 17:425-38, 1973 (33 ref.)**

ANGIOMATOSIS

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ARRHYTHMIA

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ARTERIES

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Guys Hosp Rep 121:259-62, 1972 (16 ref.)

ARTERIOSCLEROSIS

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ELECTROCARDIOGRAPHY

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EXTRASYSTOLE

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HEART

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HEART ARREST

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The science of cardiac catheterization in the diagnosis of congenital heart disease. Levin AR.
Cardiovasc Clin 4:235-73, 1973 (67 ref.)

HEART CONDUCTION SYSTEM

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Cardiovasc Clin 4:27-42, 1973 (72 ref.)
Atrioventricular junctional rhythm: classification and clinical significance. Azevodo IM de, et al.
Chest 64:732-40, Dec 73 (24 ref.)

HEART DEFECTS, CONGENITAL

Radiologic evaluation of the patient with congenital heart disease. Elliott LP.
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The regionalization of infant cardiac care in New England. Fyler DC, et al.
Cardiovasc Clin 4:339-56, 1973 (7 ref.)
Correlations of the electrocardiogram and vectorcardiogram to congenital heart disease. Guntheroth WG.
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The science of cardiac catheterization in the diagnosis of congenital heart disease. Levin AR.
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HEART SEPTAL DEFECTS, VENTRICULAR

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The role of the pediatric cardiologist in the team approach to cardiac surgery. McNamara DG.
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Current concepts of cardiac valve replacement. Senn A, et al. **Vasa 2:372-8, 1973 (25 ref.)**

HEART VALVE PROSTHESIS

Current concepts of cardiac valve replacement. Senn A, et al. **Vasa 2:372-8, 1973 (25 ref.)**

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The pharmacology of cardio-active agents. Hayes AH Jr. **Cardiovasc Clin 4:103-18, 1973 (53 ref.)**

MYOCARDIUM

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PROSTAGLANDINS

Cardiovascular-renal effects of prostaglandins: the antihypertensive, natriuretic renal "endocrine" function. Lee JB.
Arch Intern Med 133:56-76, Jan 74 (104 ref.)

PULMONARY ARTERY

Technical considerations of the microscopic evaluation of intrapulmonary vessels. Granston AS.
Ann Clin Lab Sci 3:329-34, Sep-Oct 73 (25 ref.)

PULMONARY CIRCULATION

Proceedings: Regional differences in gas exchange. Hughes JM. **Proc R Soc Med 66:974-5, Oct 73 (12 ref.)**
Proceedings: Kinetic aspects of the respiratory function of blood. Sirs JA.
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Fluid resuscitation in the severely injured. Shires GT, et al. **Surg Clin North Am 53:1341-66, Dec 73 (73 ref.)**

TETRALOGY OF FALLOT

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Am J Obstet Gynecol 117:1002-25, 1 Dec 73 (118 ref.)
Prevention of venous thromboembolism in surgical patients. Clagett GP, et al.
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Nutritional aspects of arterial disease. Macdonald I.
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VASODILATOR AGENTS

[Proceedings: Review of the cardiovascular pharmacology of perhexiline. Hudak WJ, et al.
Postgrad Med J 49:Suppl 3:16-25, Apr 73 (11 ref.)

VASOMOTOR SYSTEM

Cardiovascular-renal effects of prostaglandins: the antihypertensive, natriuretic renal "endocrine" function. Lee JB.
Arch Intern Med 133:56-76, Jan 74 (104 ref.)

VECTORCARDIOGRAPHY

Correlations of the electrocardiogram and vectorcardiogram to congenital heart disease. Guntheroth WG.
Cardiovasc Clin 4:219-33, 1973 (17 ref.)

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

APRIL TO JUNE 1974

APR. 1–10 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 4–6 **Advances in Clinical Cardiology.** Lawrence S. Cohen, FACC, director and Alfred L. Aronson, William W. L. Glenn, FACC, Allan V. N. Goodyer, FACC, Norman S. Talner, FACC and Steven Wolfson, FACC, co-directors. Yale University School of Medicine, New Haven, Conn.

APR. 17–19 **Core Curriculum—Vectorcardiography (A Basic Workshop).** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

APR. 22–25 **Current Concepts in Cardiology—1974.** Philip R. Akre, director and John A. Bowers and Masato Takahashi, FACC, co-directors. MGM Grand Hotel, Las Vegas, Nev.

MAY 6–9 **The Recognition and Management of Coronary Syndromes.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 9–11 **The Ventricular Ectopic Beat: Heart-throb or Harbinger of Death.** Bernard Tabatznik and J. O'Neal Humphries, FACC, directors. Cross Keys Inn, Baltimore, Md.

MAY 15–17 **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director. Georgetown University School of Medicine, Washington, D. C.

MAY 17–19 **Core Curriculum: Rational Drug Therapy in Cardiovascular Disease.** Robert J. Lee, PhD., director. The Nassau Inn, Princeton, N. J.

MAY 23–25 **Cardiologist's Appraisal of Operable Heart Disease.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. St. Francis Hotel, San Francisco, Calif.

JUNE 6–8 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

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New Members Elected to the College

The following individuals were elected to membership in the American College of Cardiology on January 31, 1974, in the category indicated.

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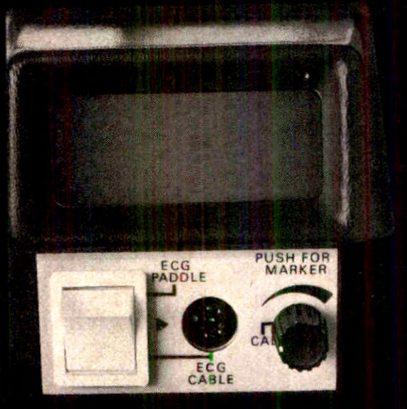

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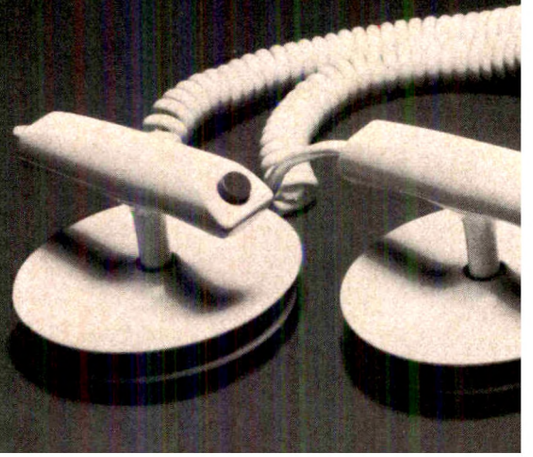

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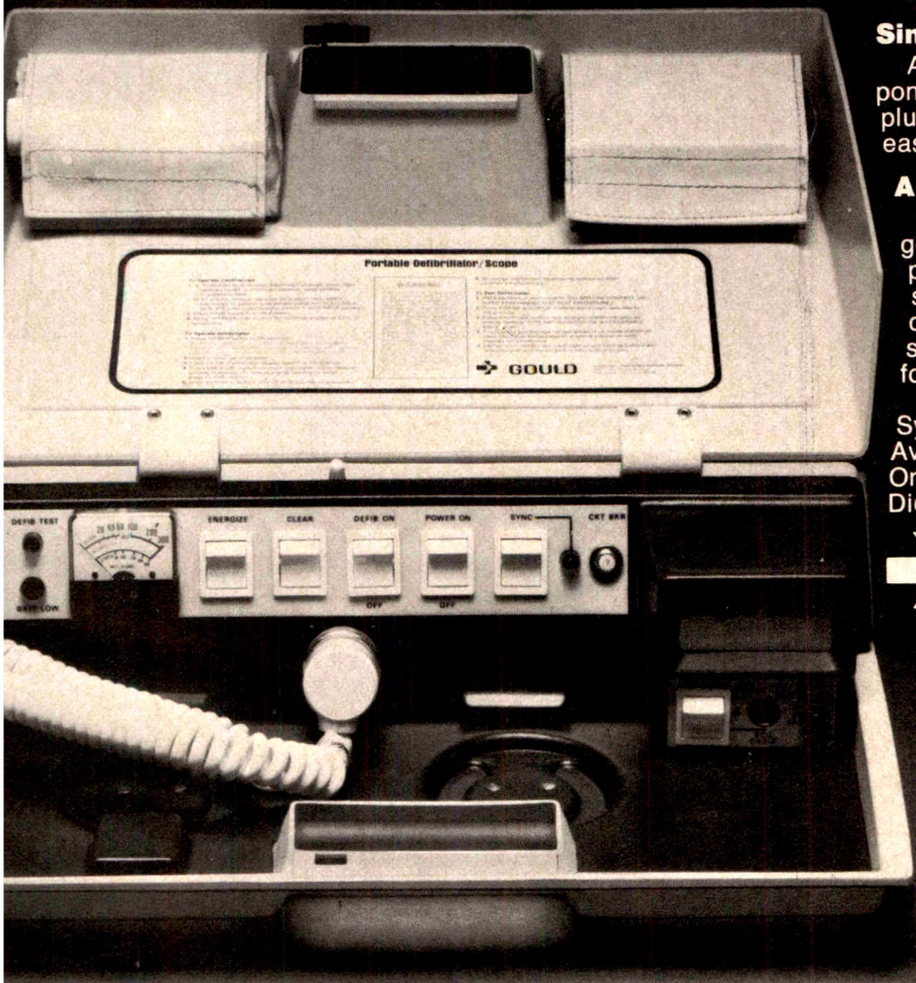

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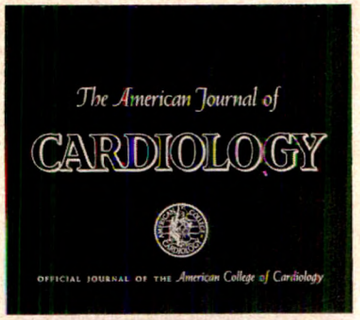

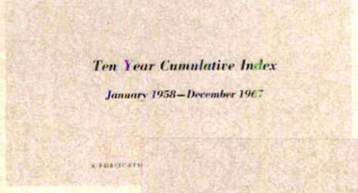

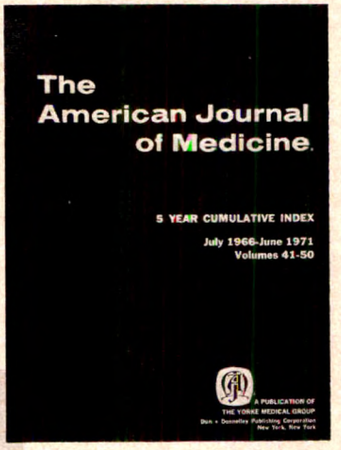

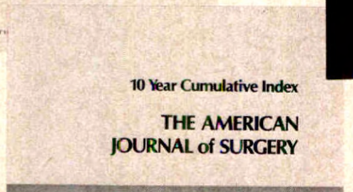

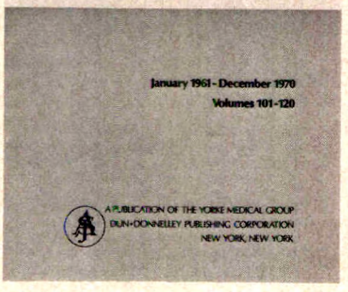

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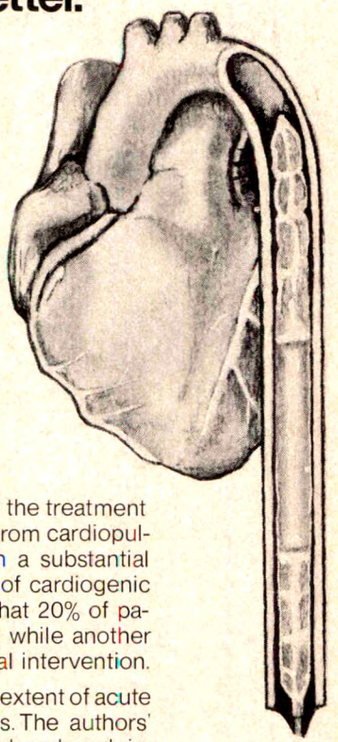

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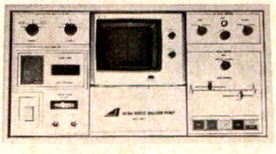

1. Editorial. JAMA 224:245. 1973.
2. Braunwald, E. and Maroko, P.R., Ann. Int. Med. 76:659. 1972.
3. Maroko, P.R. et al. Circulation 45:1150. 1972.
4. Leinbach, R.C., quoted in Emerg. Med. 5:107. 1973.
5. Buckley, M.J. et al (abstract). Circulation 46. Suppl. 2:76. 1972.
6. Dunkman, W.B. et al. Circulation 46:465. 1972.

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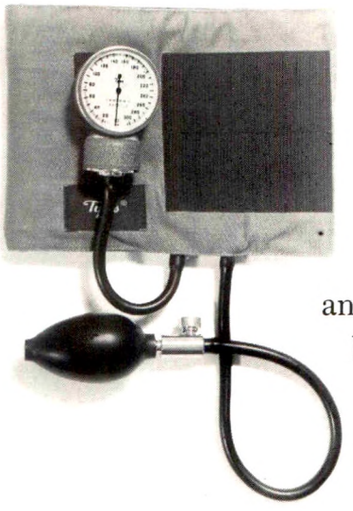

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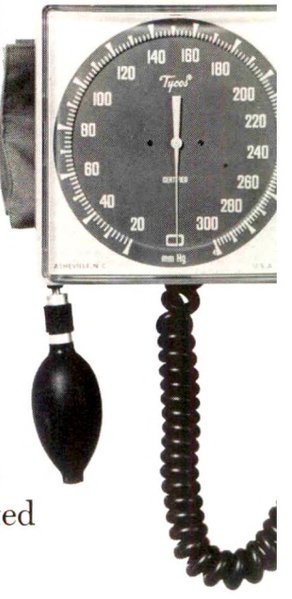

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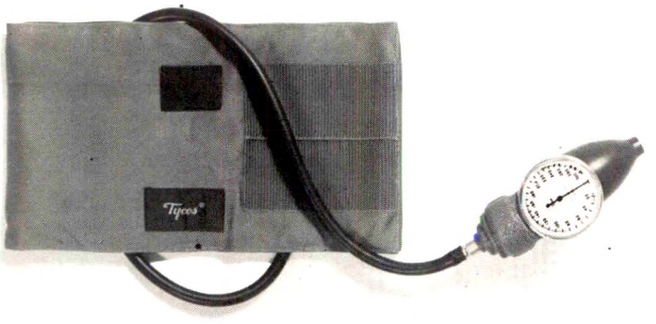

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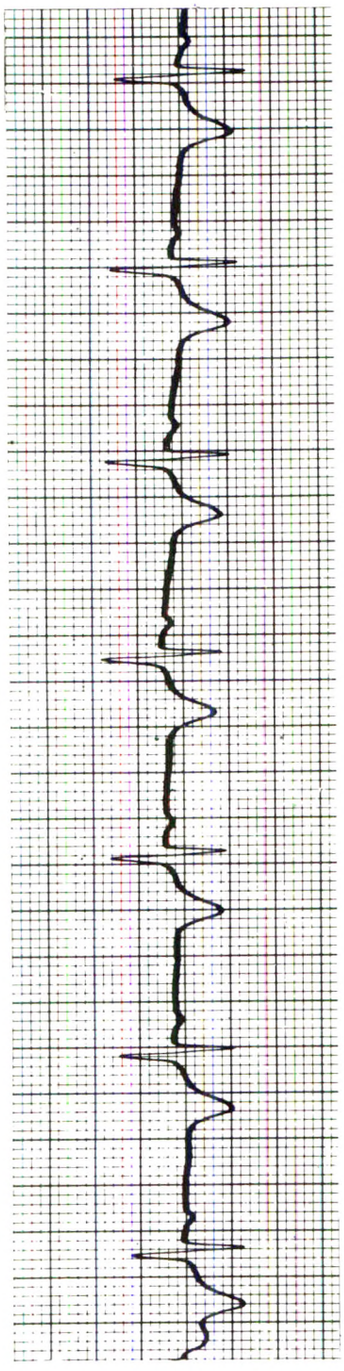

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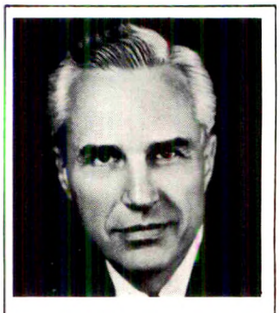

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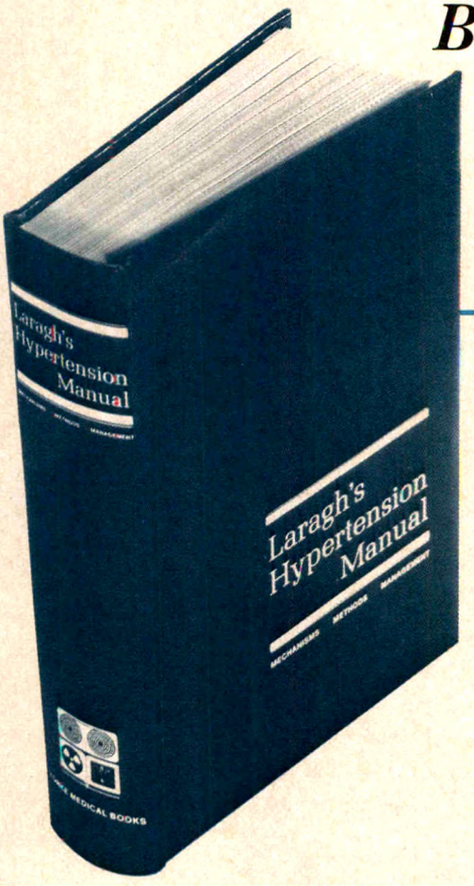

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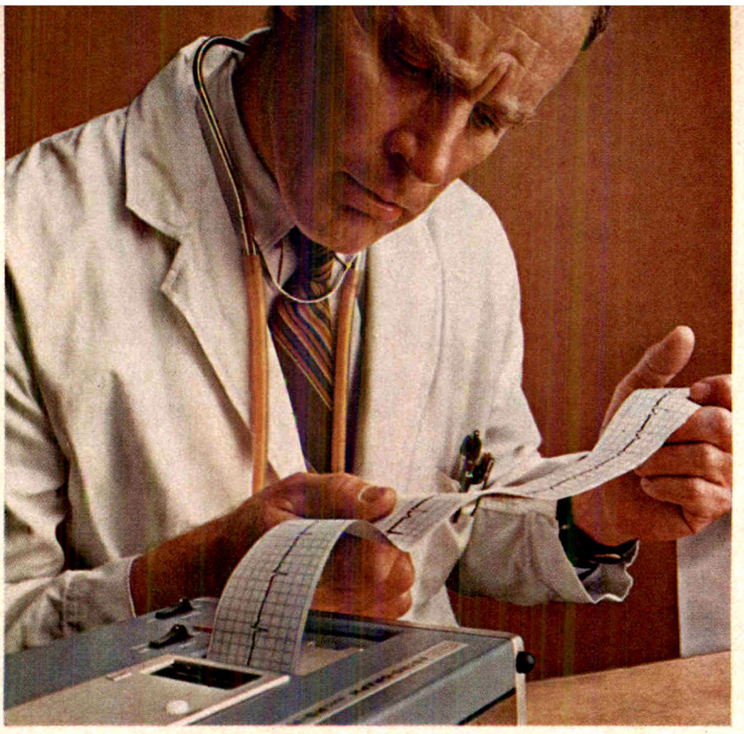

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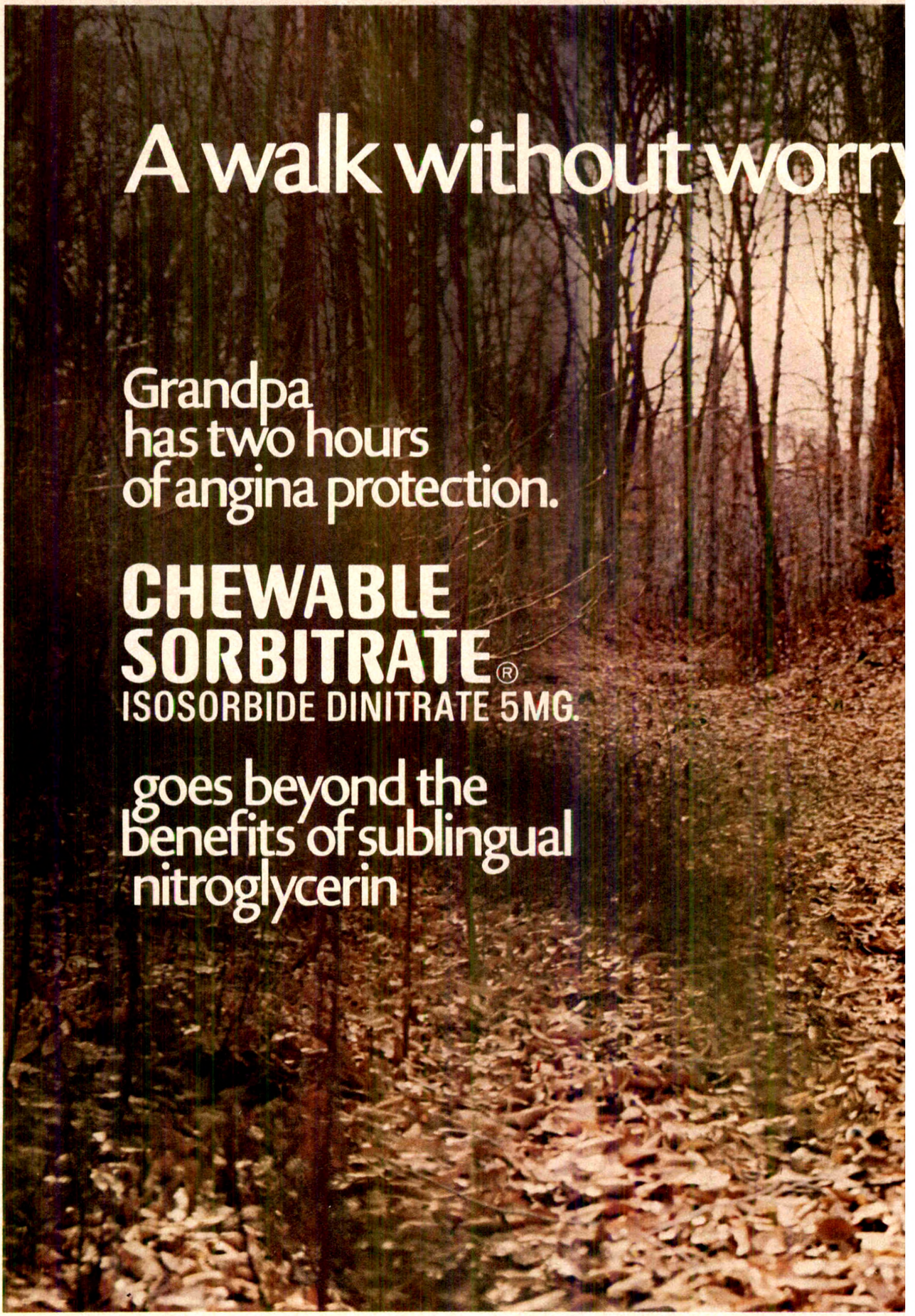
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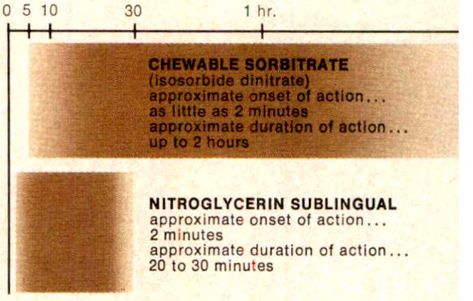

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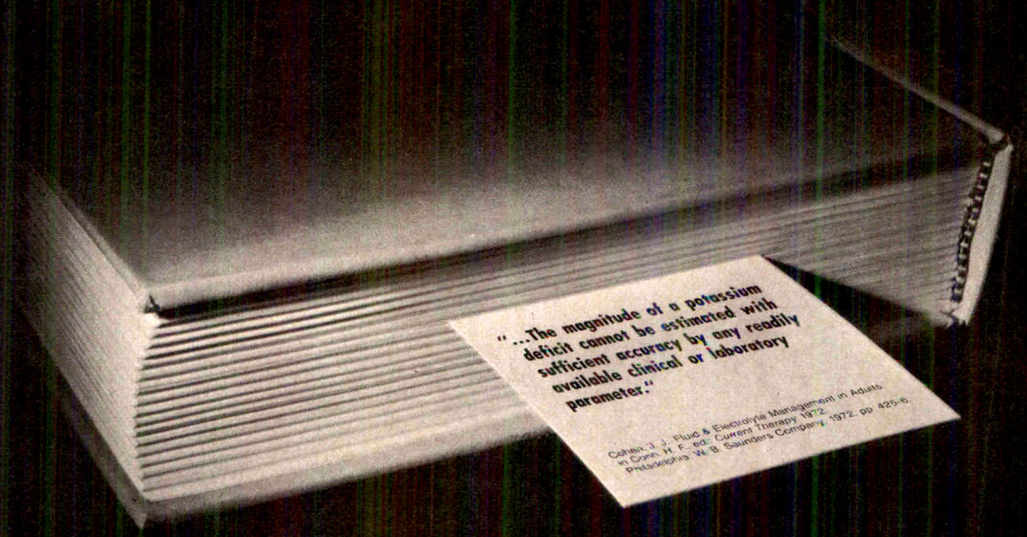

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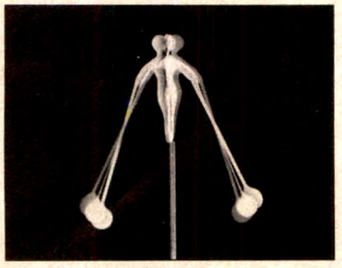

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Description: Each dry effervescent tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., l-lysine hydrochloride 0.913 g. Solution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate, and l-lysine hydrochloride.

Indications: For prevention or correction of potassium depletion and hypokalemic alkalosis. Especially useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each tablet completely in the stated amount of water.

Adverse Reactions: Vomiting, diarrhea, nausea and abdominal discomfort may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, and tall, peaked T waves.

Dosage and Administration: Adults: 1 tablet (20 mEq. each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water 2 to 4 times daily depending upon the requirements of the patient. The approximate minimum adult daily requirement of potassium is 40 mEq. Deviations from this recommendation may be indicated, since no average total daily dose can be defined but must be governed by close observation for clinical effects.
NOTE: Klorvess should be taken with meals.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

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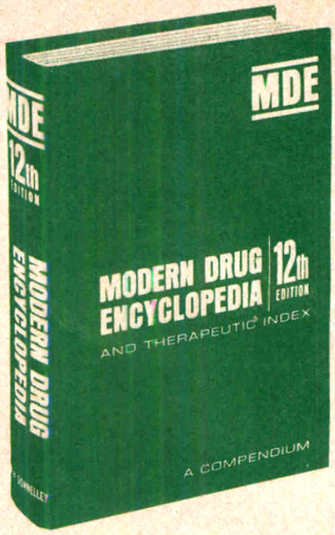

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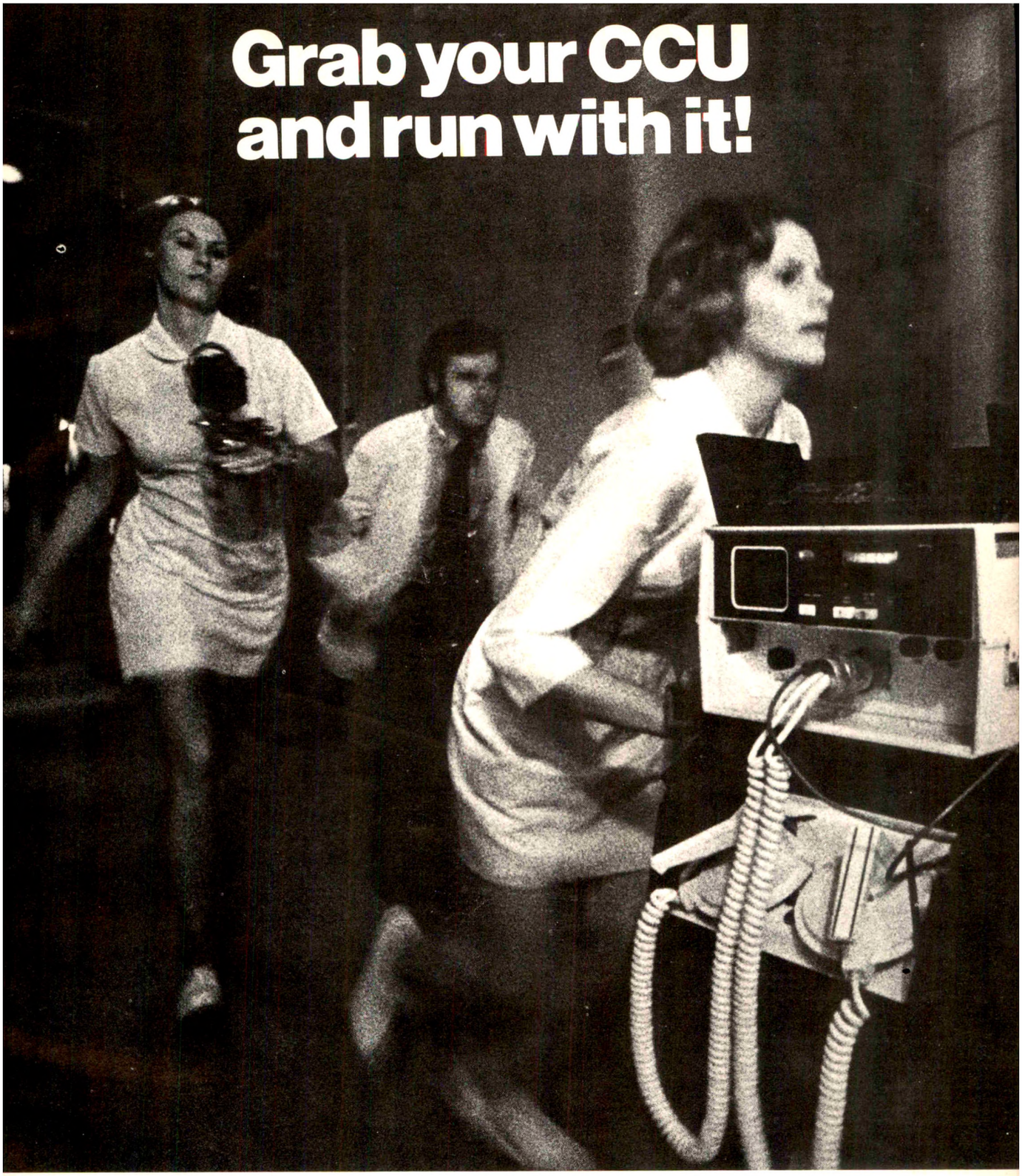

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AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

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CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
SIDE EFFECTS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
DOSAGE AND ADMINISTRATION: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
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MAY 6, 1974

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Electrophysiologic Properties of Antiarrhythmic Agents

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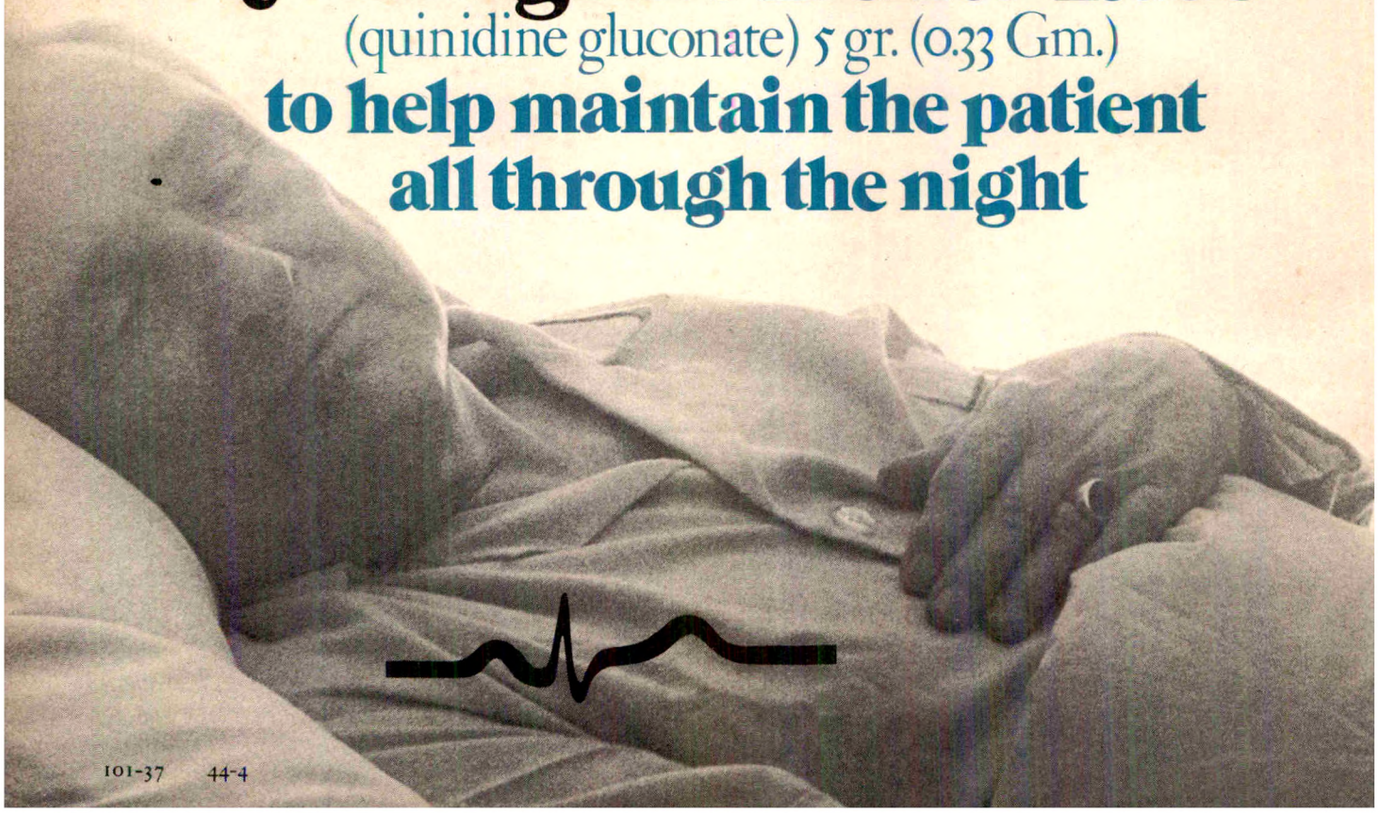

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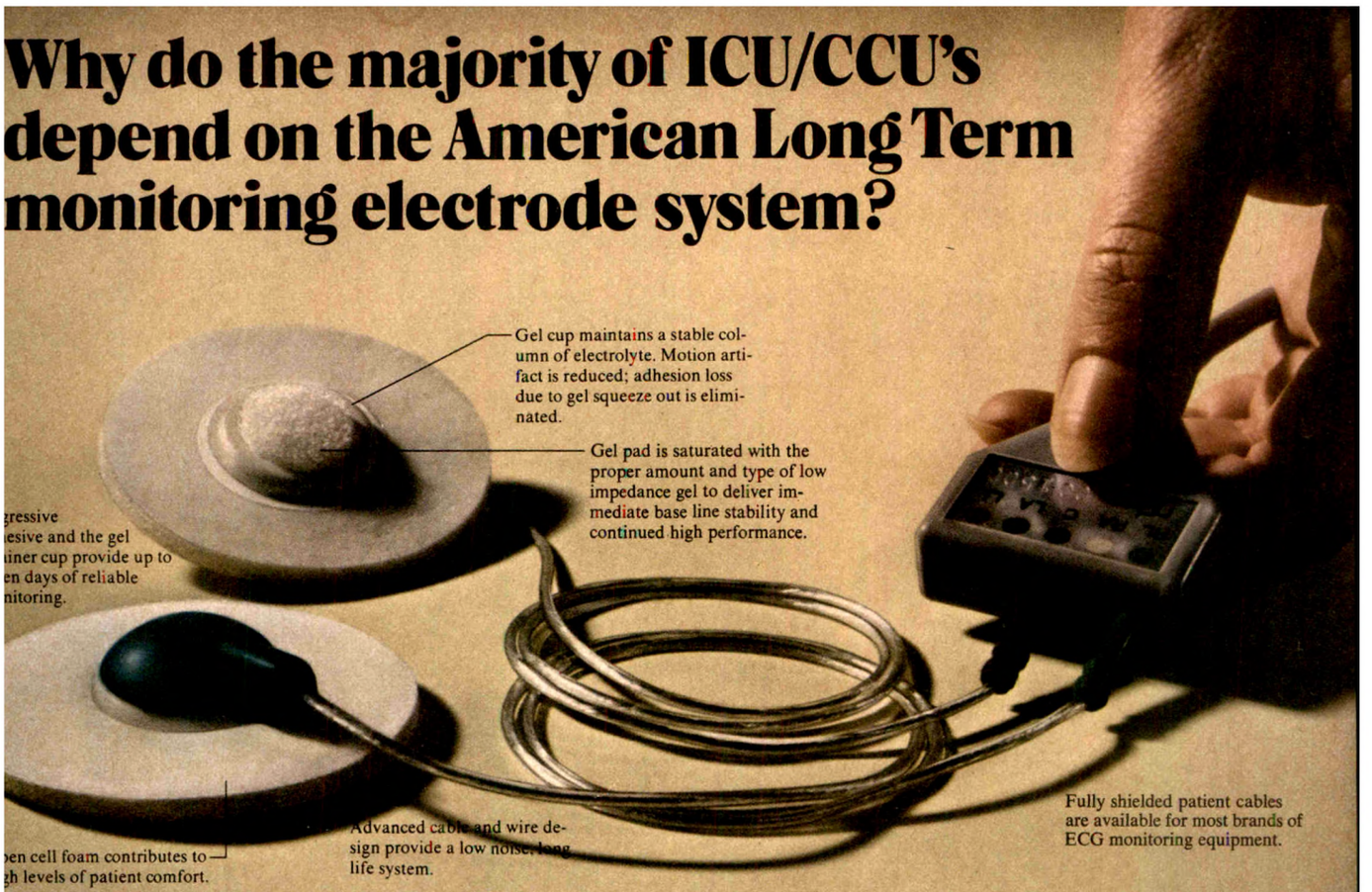

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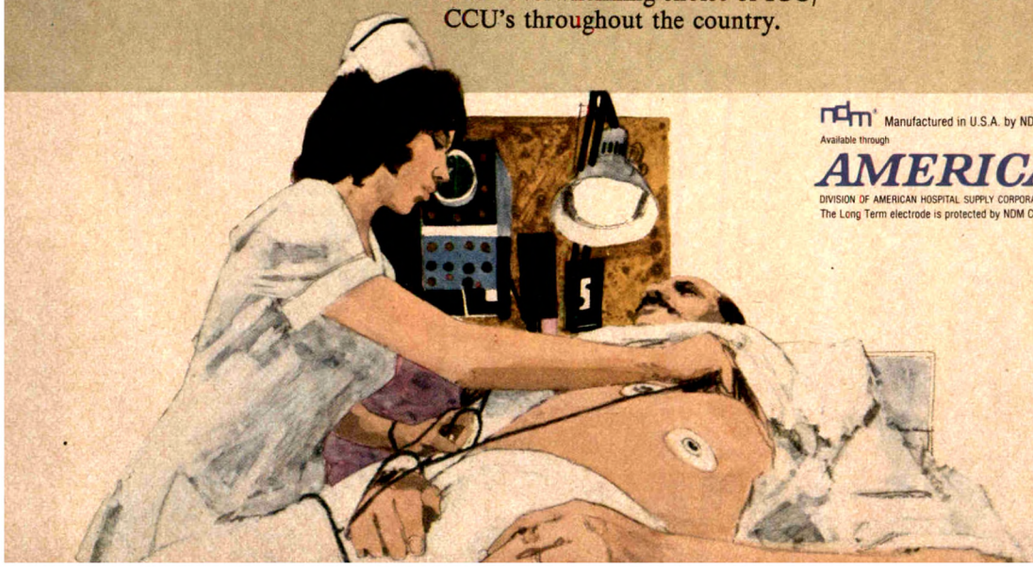

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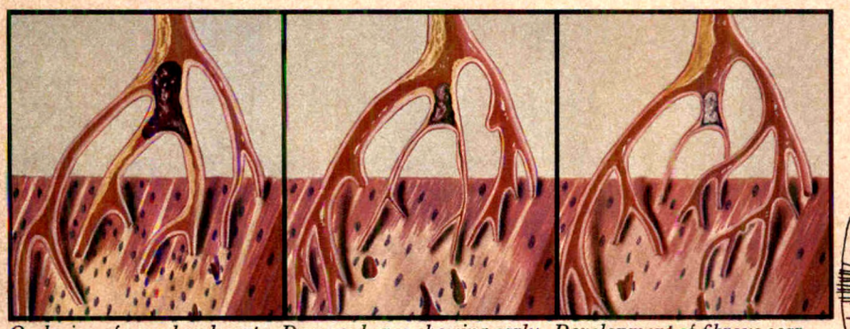
As the infarct heals,



Occlusion of vessel and acute infarct of the myocardium.

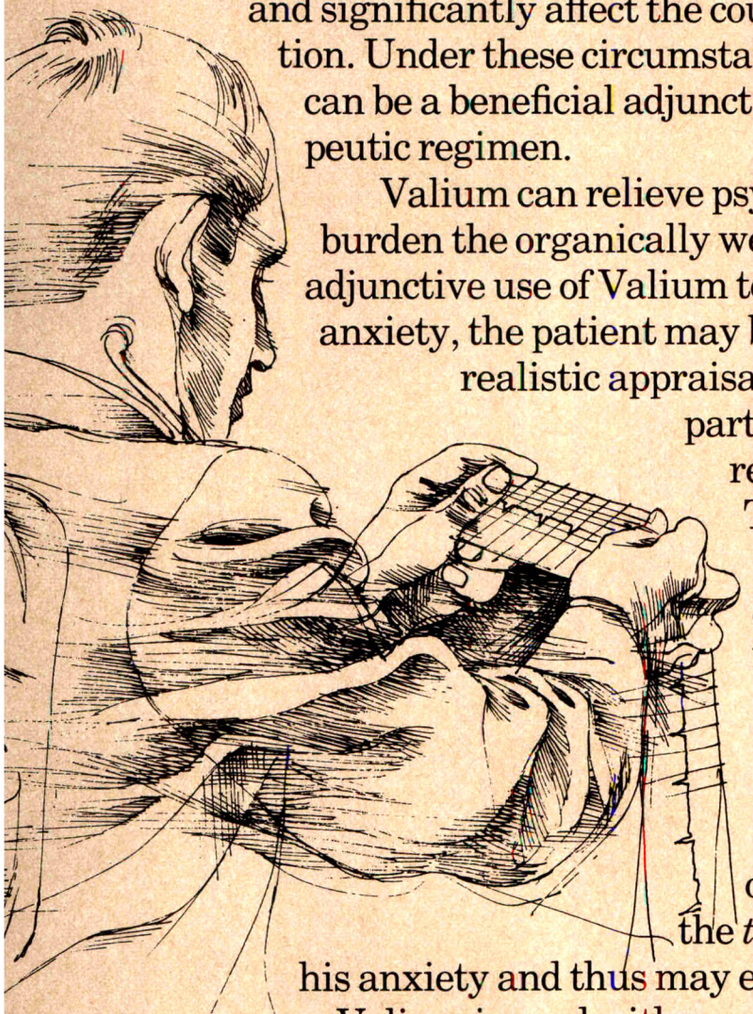
Damaged area showing early collateral vessel formation.

Development of fibrous scar and healing of infarcted area.

will psychic tension affect the patient's rehabilitation?

ROCHE

After the MI patient's acute episode has been successfully managed, a program of rehabilitation is begun. At times the overly tense cardiac patient may present a special problem. Although you continue to encourage a positive outlook through counseling and enlistment of support from the patient's family, psychic tension may remain, and significantly affect the course of rehabilitation. Under these circumstances, Valium (diazepam) can be a beneficial adjunct to the patient's therapeutic regimen.



Valium can relieve psychic tension that may burden the organically weak heart. As a result of adjunctive use of Valium to relieve unwarranted anxiety, the patient may be able to arrive at a more realistic appraisal of his situation and participate more fully with his rehabilitation program.

Therapy should normally be continued until the patient's anxiety has been reduced to tolerable levels.

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Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticholinergics and antacids. The most commonly reported side effects have been drowsiness, fatigue and ataxia. Patients taking Valium should be cautioned against driving or operating dangerous machinery.

Valium®(diazepam)
2-mg, 5-mg, 10-mg tablets

when you consider it essential to keep the heart patient calm

Please turn page for a summary of product information.

When you consider it essential to keep the heart patient calm

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- Valium works promptly in most patients. Significant improvement is usually noted during the first few days of therapy, although some patients may require more time to respond.
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- Valium has a wide margin of safety in the usual oral dosage range and generally does not significantly affect respiration or pulse.

Valium® (diazepam) 2-mg, 5-mg, 10-mg tablets

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Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

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Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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THE AMERICAN JOURNAL OF CARDIOLOGY,® Official Journal of the American College of Cardiology, May 6, 1974, Vol 33, No. 5.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except May and October, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group, William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES: 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

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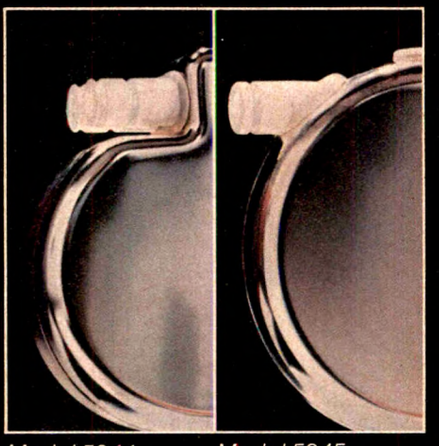

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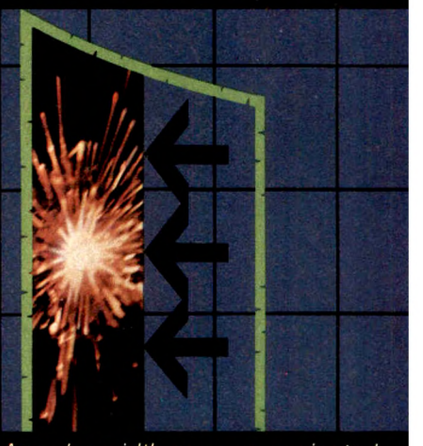

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CLINICAL STUDIES

583 Bundle Branch Block. Demonstration of the Incomplete Nature of Some "Complete" Bundle Branch and Fascicular Blocks by the Extrastimulus Technique

DELON WU, PABLO DENES, RAMESH DHINGRA and KENNETH M. ROSEN

These electrophysiologic studies using the atrial extrastimulus technique in three patients demonstrate that partial bundle branch block depends on a discordance of conduction time and refractory period. The bundle or fascicle with depressed conduction has a shorter refractory period than the more normally conducting bundle or fascicle. The data suggest that incomplete blocks can occur in the three fascicles and may predispose to development of trifascicular block with a normal H–V interval and to aberrant conduction during supraventricular tachyarrhythmias.

590 Concealed Bypasses of the Atrioventricular Node in Patients with Paroxysmal Supraventricular Tachycardia Revealed by Intracardiac Stimulation and Verapamil

ROWORTH A. J. SPURRELL, DENNIS M. KRIKLER and EDGAR SOWTON

Acting predominantly on antegrade and retrograde conduction in the atrioventricular node, verapamil (10 mg) given intravenously terminated paroxysmal supraventricular tachycardia in all 13 patients. The minimal effect of this drug on retrograde conduction and the minimal increase in retrograde conduction during ventricular pacing in five of the patients suggested the presence of an A–V nodal bypass not apparent from the surface electrocardiogram.

596 Electrophysiologic Properties of Procainamide in Man

MARK E. JOSEPHSON, ANTHONY R. CARACTA, MICHAEL A. RICCIUTTI, SUN H. LAU and ANTHONY N. DAMATO

Procainamide given to 16 patients with sinus rhythm minimally prolonged atrioventricular (A–V) conduction in 11 subjects and significantly prolonged His-Purkinje conduction time in 15. The effective refractory period of the A–V node decreased in eight of nine patients. The relative refractory period of the His-Purkinje system was prolonged in 10 of 11 patients.

604 Arrhythmias After Cardiac Transplantation

JOHN S. SCHROEDER, DAVID K. BERKE, ANTHONY F. GRAHAM, ALAN K. RIDER and DONALD C. HARRISON

Atrial arrhythmias were noted in 72 percent and ventricular premature contractions in 57 percent of 45 cardiac allograft recipients. Two patients had ventricular fibrillation. Antiarrhythmic agents, cardioversion or treatment of the underlying rejection process controlled these cardiac irregularities. These interesting observations indicate autonomic innervation of the heart is neither a prerequisite for the development of cardiac arrhythmias nor a requirement for a successful response to antiarrhythmic therapy.

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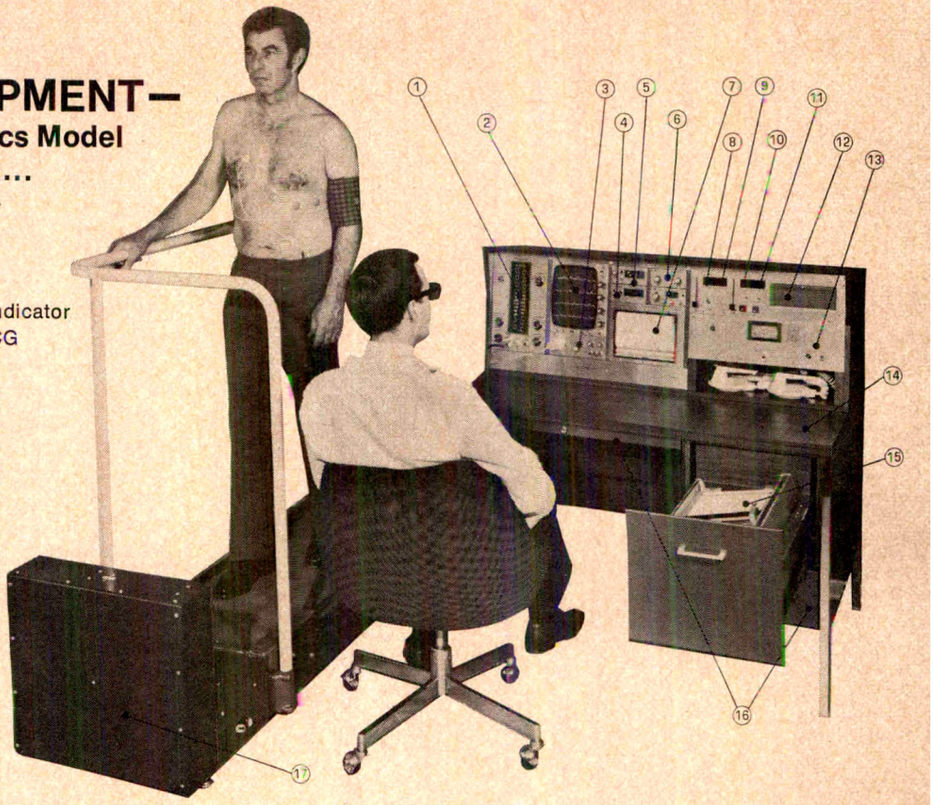

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608 Criteria for Electrocardiographic Differentiation of Right Ventricular Hypertrophy from True Posterior Myocardial Infarction

P. MANOHAR KINI and HUBERT V. PIPBERGER

A Q/R ratio greater than 0.25 in lead Y led to the recognition of 51 percent of cases of posterior wall myocardial infarction and proved the most useful criterion in this study to differentiate true posterior wall myocardial infarction from right ventricular hypertrophy. With seven measurements obtained in multivariate analysis 78 percent of cases of posterior myocardial infarction and 79 percent of cases of right ventricular hypertrophy were correctly classified.

614 Comparative Prevalence of the Fourth Heart Sound in Hypertensive and Matched Normal Persons

MICHAEL SWISTAK, HARRY MUSHLIN and DAVID H. SPODICK

This blind, randomized phonocardiographic study of 50 normal and 50 age- and sex-matched hypertensive subjects showed a high and equal prevalence rate of S_4 in middle-aged persons as in older persons. Quantitative studies are indicated to determine when this sound can be considered a presystolic gallop.

EXPERIMENTAL STUDIES

617 Sinus Nodal Reentry. Effect of Quinidine

KARLEN L. PAULAY, GERALD M. WEISFOGEL and ANTHONY N. DAMATO

Sinus nodal reentry experimentally produced in 19 dogs was abolished by therapeutic blood levels of quinidine which increased atrial refractoriness and slowed atrial conduction in 15 dogs and also induced conduction delay and block along the reentrant pathway in 6 of the animals. Such delay and block may be another mechanism for abolishing sinus nodal reentry.

623 Functional Anatomy of the Canine Left Bundle Branch

RALPH LAZZARA, BILLY K. YEH and PHILIP SAMET

Anatomic and electrophysiologic data obtained in vitro before and after lesions were placed in the proximal left bundle branch of the heart in 11 dogs suggest that this branch is best represented as a fan-shaped network of interwoven fibers whose diverging border fibers are specialized for rapid, distant transport. The clinical implications with reference to the bifascicular representation of the human left bundle branch are discussed.

633 Electrophysiologic Antagonism of Quinidine and Bretylium Tosylate

IRANY M. DE AZEVEDO, YOSHIO WATANABE and LEONARD S. DREIFUS

Administration of quinidine and bretylium tosylate in isolated perfused rabbit hearts demonstrated contrasting electrophysiologic effects of these agents on atrioventricular conduction and the duration of action potential and the refractory period in ventricular fibers. The results suggest that use of bretylium to control arrhythmias may require withdrawal of other antiarrhythmic agents.

639 Effects of Intraperitoneal Administration of Propranolol on the Mouse Heart. Histochemical and Electron Microscopic Observations

EDGAR F. ALLIN, JANICE M. MILLER, GEORGE G. ROWE and JAMES A. WILL

Ultrastructural and histochemical studies showed no acceptable evidence that propranolol caused myocardial damage in 3 week old Swiss white mice, negating earlier reported evidence that propranolol produces cardiac lesions.

Continued on page A15

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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643 Computerized System for Noninvasive Techniques. I. Its Value for Systolic Time Intervals

SAMUEL ZONERAICH, OLGA ZONERAICH and JOHN RODENRYS

Use of a total computerized system described in this article for the study of noninvasive techniques can more rapidly and accurately calculate many variables and lead to better evaluation of left ventricular function.

650 Quantification of Serum Creatine Phosphokinase Isoenzyme Activity

ROBERT ROBERTS, PHILIP D. HENRY, SAKE A. G. J. WITTEEVEEN and BURTON E. SOBEL

This new procedure to determine quantitatively activity of individual creatine phosphokinase (CPK) isoenzymes in a serum sample with or without increased total CPK activity appears particularly useful in assessing myocardial infarction. Serum MB CPK activity averaged 0.002 IU/ml in 27 normal persons, 0.064 IU/ml in 30 subjects with myocardial infarction and was not increased in 23 patients after intramuscular injection or abdominal surgery.

REPORTS ON THERAPY

655 Prophylactic Quinidine for the Prevention of Arrhythmias After Acute Myocardial Infarction

DAVID T. JONES, WILLIAM J. KOSTUK and RAMSAY W. GUNTON

This reappraisal of the value of prophylactic orally administered quinidine in 103 patients with uncomplicated myocardial infarction of less than 24 hours' duration shows that over the observation period of 72 hours ventricular arrhythmias occurred in 45 percent of the 58 patients receiving placebo and in 16 percent of those receiving quinidine. Ventricular tachycardia occurred in 12 of 58 patients receiving placebo and in only 1 of 45 quinidine-treated patients. There was no difference in mortality in either group during the 72 hour study or during the entire period of hospitalization.

661 Comprehensive Treatment Plan for the Prevention of Primary Ventricular Fibrillation in Acute Myocardial Infarction

MILFORD G. WYMAN and LUCILLE HAMMERSMITH

Prophylactic administration of lidocaine or procainamide, or both, according to a carefully prescribed plan upon a patient's admission to the emergency room and coronary care unit of a community hospital lowered the prevalence rate of primary ventricular fibrillation from 6.5 percent of 139 cases to 0.3 percent and no deaths in 1,026 cases.

PEDIATRIC CARDIOLOGY

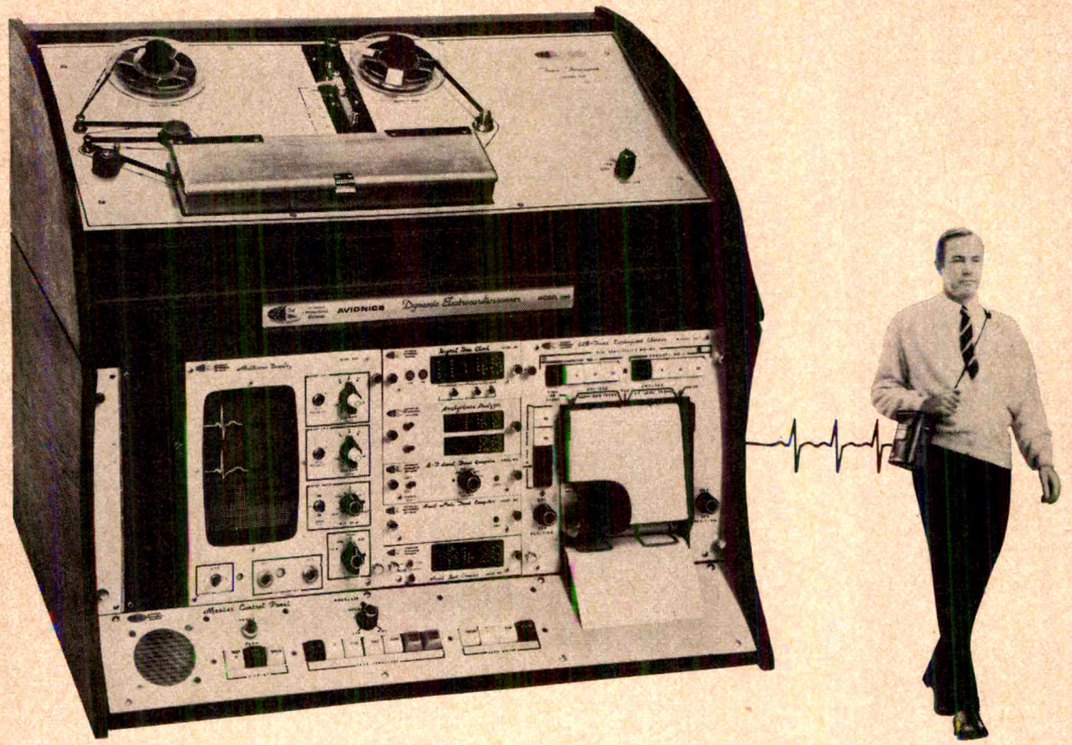
668 Ostium Secundum Atrial Septal Defect Associated with Balloon Mitral Valve in Children

BENJAMIN E. VICTORICA, LARRY P. ELLIOTT and IRA H. GESSNER

These studies in eight patients indicate a balloon mitral valve should be suspected in all children with an ostium secundum atrial septal defect and particularly those with unusual electrovectorcardiographic features or suggestive auscultatory findings such as a midsystolic click or a late systolic murmur of mitral insufficiency. Left ventriculograms in every patient with an atrial septal defect are recommended to determine the status of the mitral valve.

Continued on page A17

THE NEW 660 A DRAMATIC LEAP FORWARD IN DYNAMIC ELECTROCARDIOGRAPHY!



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Del Mar Engineering Laboratories, 6901 West Imperial Highway, Los Angeles, Calif. 90045/Phone: (213) 641-7700

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674 Cyanosis in Patients with Atrial Septal Defect Due to Systemic Venous Drainage into the Left Atrium

MAXWELL S. MAILLIS, TSUNG O. CHENG, JERRY F. MEYER, I. SYLVIA CRAWLEY and JOSEPH LINDSAY, Jr.

Three patients with atrial septal defect had cyanosis and significant left to right shunting due to systemic venoarterial shunting into the left atrium. Since cyanosis is not a contraindication to surgical closure of the septal defect in such patients, diagnostic cardiac catheterization studies should be performed to detect this less well recognized mechanism.

PROGRESS REPORTS

679 Patency of Aortocoronary Vein Grafts and Serum Triglycerides. Three Year Follow-Up Study

CLAUDE ALLARD, CLAUDE GOULET, CLAUDE M. GRONDIN, JACQUES LESPERANCE and MARTIAL BOURASSA

This 3 year study demonstrates an increased risk of occlusion or stenosis of aortocoronary vein grafts in patients with hypertriglyceridemia. Serum cholesterol levels did not affect the fate of these grafts.

CASE REPORTS

681 Chordae Tendineae Rupture Complicating the Systolic Click-Late Systolic Murmur Syndrome

DORIS GOODMAN, DEMETRIOS KIMBIRIS and JOSEPH W. LINHART

Acute mitral insufficiency occurring after spontaneous rupture of mitral chordae tendineae belies the commonly accepted benignity of the systolic click-late systolic murmur syndrome. This complication in a 52 year old woman necessitated the insertion of a mitral valve prosthesis and led to her death from hypotension, bradycardia and bleeding several days after operation.

685 Diastolic Blood Flow Into the Pulmonary Artery in Carcinoid Heart Disease

PAUL M. WOLFSON, LOTFY L. BASTA, RICHARD P. SNODGRASS and J. MICHAEL KIOSCHOS

Diastolic blood flow into the pulmonary artery is attributed to the combined effects of increased right atrial pressure, decreased right ventricular compliance and normal pulmonary arterial pressure in this 45 year old patient with carcinoid heart disease.

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689 Calcium Responses ("Calcium Spikes")

BORYS SURAWICZ

SPECIAL DEPARTMENTS

691 Letters to the Editor

Hemodynamics in Myocardial Infarction—Rahimtoola
Medically Uncontrollable Ventricular Tachyarrhythmia in Association with Ventricular Aneurysm—Liotta et al.

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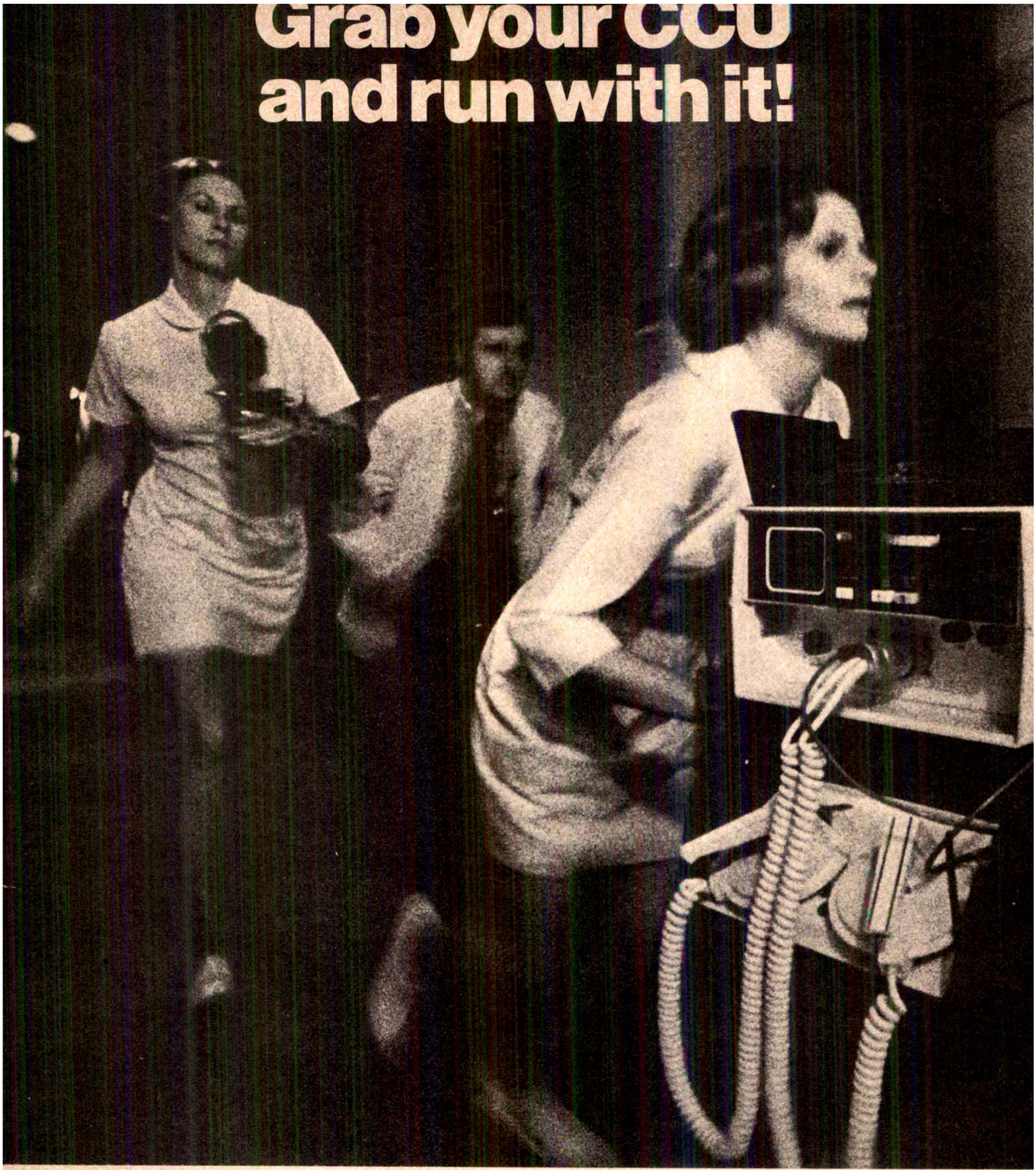
Grab your CCU and run with it!



It would be ideal if you could confine all cardiac arrest cases to the Coronary Care Unit . . . where they could be treated immediately. The trouble is, they can and do happen anywhere in the hospital.

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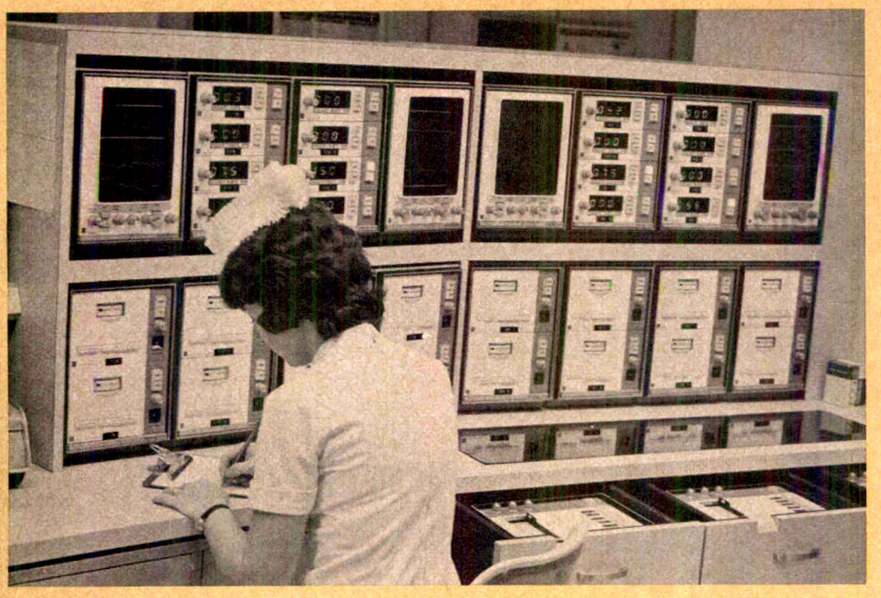


Large Hospital Chooses Single Manufacturer For Its Patient Monitoring Equipment

One of the nation's comprehensive patient monitoring facilities is located in a 620-bed northern Ohio hospital. Here, 53 beds are electronically monitored for heart attack victims, the critically ill, and trauma patients. All monitoring equipment is General Electric, with the exception of 16 beds installed several years earlier.

Cardiac Care

In the cardiac care unit, GE monitoring equipment includes an ECG amplifier, heart rate module, and single channel display at each of 16 beds. The central nurse station is equipped with remote heart rate and arrhythmia monitors for each of these beds. In addition the nurse station also has four 4-trace nonfade displays with a 12-second memory and ECG "freeze" mode, three AHA automatic graph recorders, and a portable graph recorder for use at bedside.

According to the CCU division manager, "The nonfade displays with built-in alarms have been a big help. We can freeze any of the 16 patient's baselines, look at any particular complex, hold it indefinitely, and write out the information at any given time afterwards. The nonfade feature lets us hold information for more extensive study while maintaining a complete record."

Post-cardiac care

The 25-bed post-cardiac care unit serves ambulatory patients requiring only intermediate care, following their transfer from the CCU. This unit is equipped with GE telemetry systems. Patients are free to move about within the area while small transmitters, attached to their chests, transmit ECG data to the unit's nurse station.

At this station, up to four ECG transmissions are monitored on a single 4-trace nonfade display. Heart rate information is presented by four digital heart rate displays. The system has automatic visual and audible alarms to alert the staff if preset limits are exceeded. A single graph recorder serves four patients, and automatically switches to the appropriate channel in an alarm condition. An additional portable, battery-powered telemetry system is available for use at bedside, or to monitor a fifth patient.

Intensive care

At each bedside in the 12-bed intensive care unit there is an ECG amplifier, heart rate module, single-trace display, and digital temperature readout. Four mobile carts provide bedside monitoring of venous and arterial blood pressures; blood pressures for an 8-bed section can be remotely displayed at the central nurse station.

The central station in ICU features three 4-trace, nonfade displays, remote digital heart rate monitors, and three automatic graphs. ICU division manager states that the large work load required "an easy-to-use, highly-accurate monitoring system." Another consideration, he adds, "was the likelihood of an eventual move to a more convenient location. The modular design of the GE equipment will make that a relatively simple job.

GENERAL ELECTRIC

The burn unit and hemodialysis units, located adjacent to the ICU, are equipped with identical emergency carts consisting of an ECG amplifier, heart rate monitor, single-channel scope, graph, recorder, and DC defibrillator.

Emergency department

The hospital's emergency department is furnished with two mobile telemetry monitoring systems, comprising a telemetry receiver, heart rate monitor, graph recorder, and a 2-trace nonfade display with 12-second memory.

The division manager of the emergency department says, "On an average, we are using the telemetry system approximately 10 times during each 24-hour period. Each patient monitored is on the system for about two hours." He adds, "We routinely monitor all patients admitted who exhibit any indication of possible heart problems, therefore, increasing our capability of providing anticipatory care."

All telemetry information is duplicated at the central nurse station, eliminating any need to keep medical personnel in constant attendance at bedside. The station is equipped with a 4-trace, nonfade display. The display is operated in the "cascade" mode, thus 12 seconds of ECG data for each of two patients is always on view.

Why GE Equipment?

The hospital's CCU division manager, who coordinated monitoring equipment acquisition explains:

"We knew we wanted to buy all the equipment from a single manufacturer. With only one manufacturer's equipment throughout the house, training problems are simplified. And because we were changing from one system to another, the quality of in-service education offered was important," he adds.

"Our GE representative spent an extensive amount of time in the hospital developing a program to instruct nurses in the application of the equipment. We've had two sessions of in-service education of four days each, involving about 150 hospital personnel, with future programs planned," he says.

"We also considered maintenance of the equipment. When you have as many patients monitored as we do, time is very important.

"The GE service technicians give us service at a moment's notice. If a problem does occur, the modular design permits repairs to be performed quickly.

"We believe the nursing staff must feel very confident with a monitoring system, and they do feel confident with GE's. The equipment has few controls to adjust, and doesn't require extensive set-up procedures by the nurses."

Total Involvement from Beginning to Present

The planning staff of a 518-bed medical center, located in the far northwestern corner of the country, reports that total and early involvement of the manufacturer was of immeasurable help in getting its coronary care area designed, equipped and functioning on schedule.

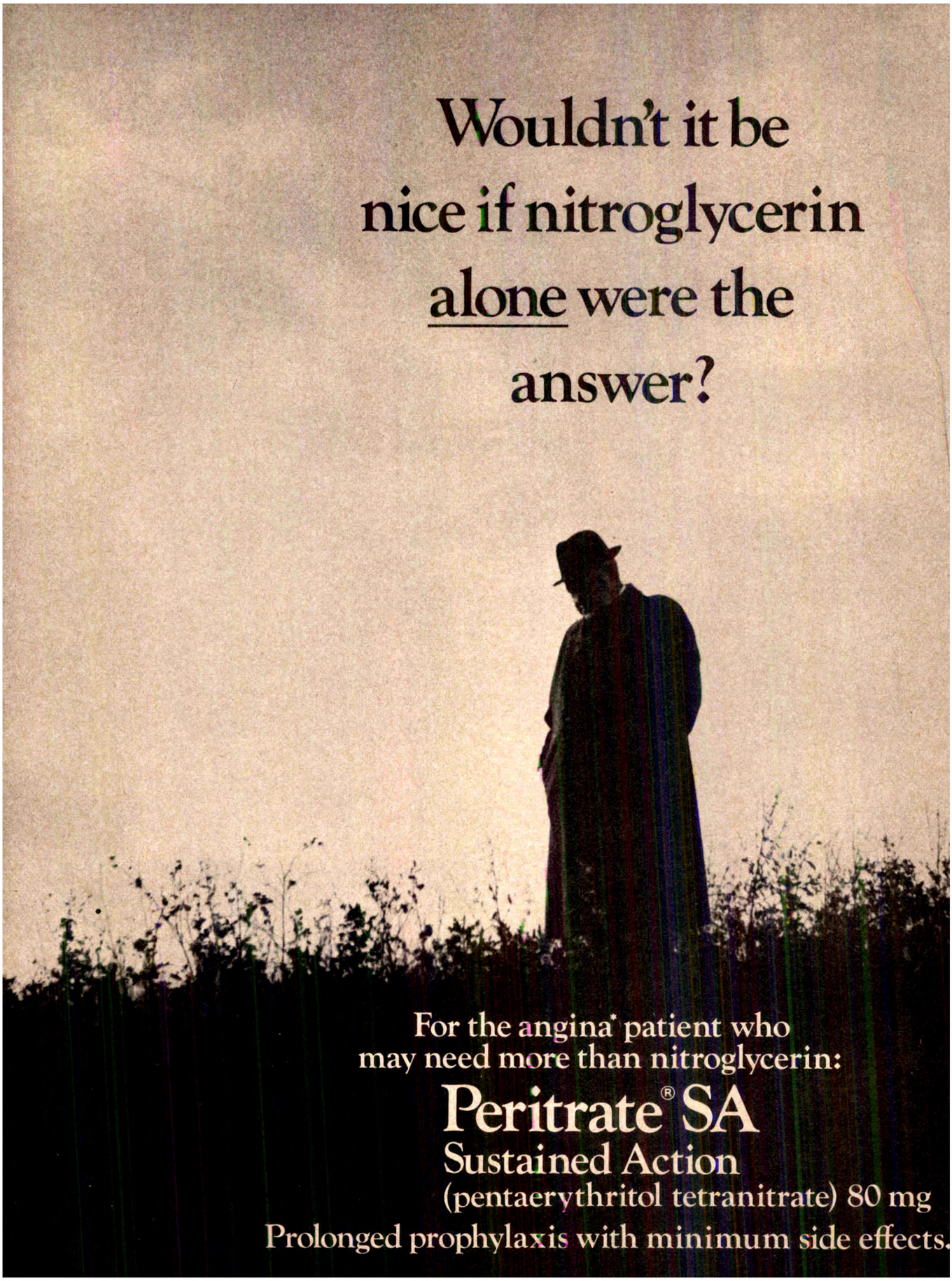
The department called for 10 monitored beds of acute coronary care, and 6 beds of monitored telemetry in intermediate coronary care, with capabilities of expanding to 20 beds. Intensive care was to include 4 monitored beds, with expansion capabilities to 12 beds.

The nurse station comprised 4-trace, nonfade displays and automatic graphs. Each room was equipped with an ECG amplifier, master heart rate and 2-trace nonfade display. General Electric patient monitoring was specified throughout.

Manufacturer participation, through GE's Northwest District, began soon after the building decision was made. Under the supervision of this District, GE architectural, electrical and biomedical engineers were involved in the actual installation of the equipment.

As part of the service contract, a GE Medical Systems serviceman is assigned to the center on a full time basis, servicing the coronary care area and the 30-room radiology department.

General Electric
Medical Systems
Milwaukee, Toronto,
Liege, Madrid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Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later.

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Additional Dosage Forms: Peritrate 20 mg–light green, scored tablets; Peritrate 10 mg–light green, unscored tablets. Bottles of 100 and 1000. Full information is available on request.

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PE-GP-41

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THERMODILUTION

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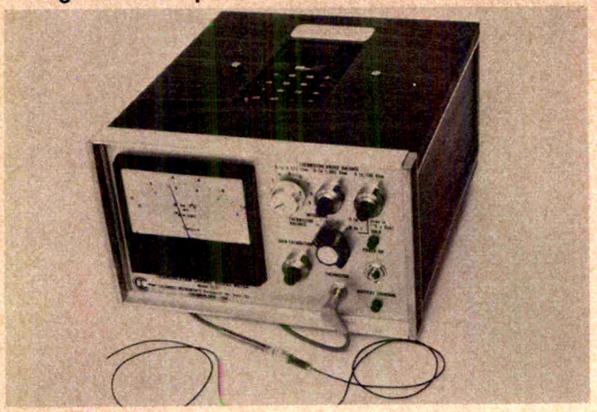

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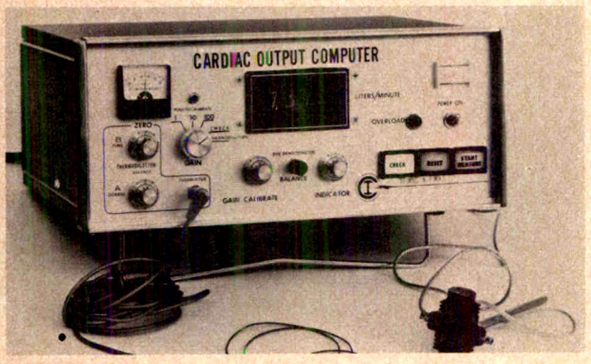

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone; routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May be additive or potentiative of the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Usage in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in cord blood and breast milk. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; single-dose blister packs, boxes of 500.

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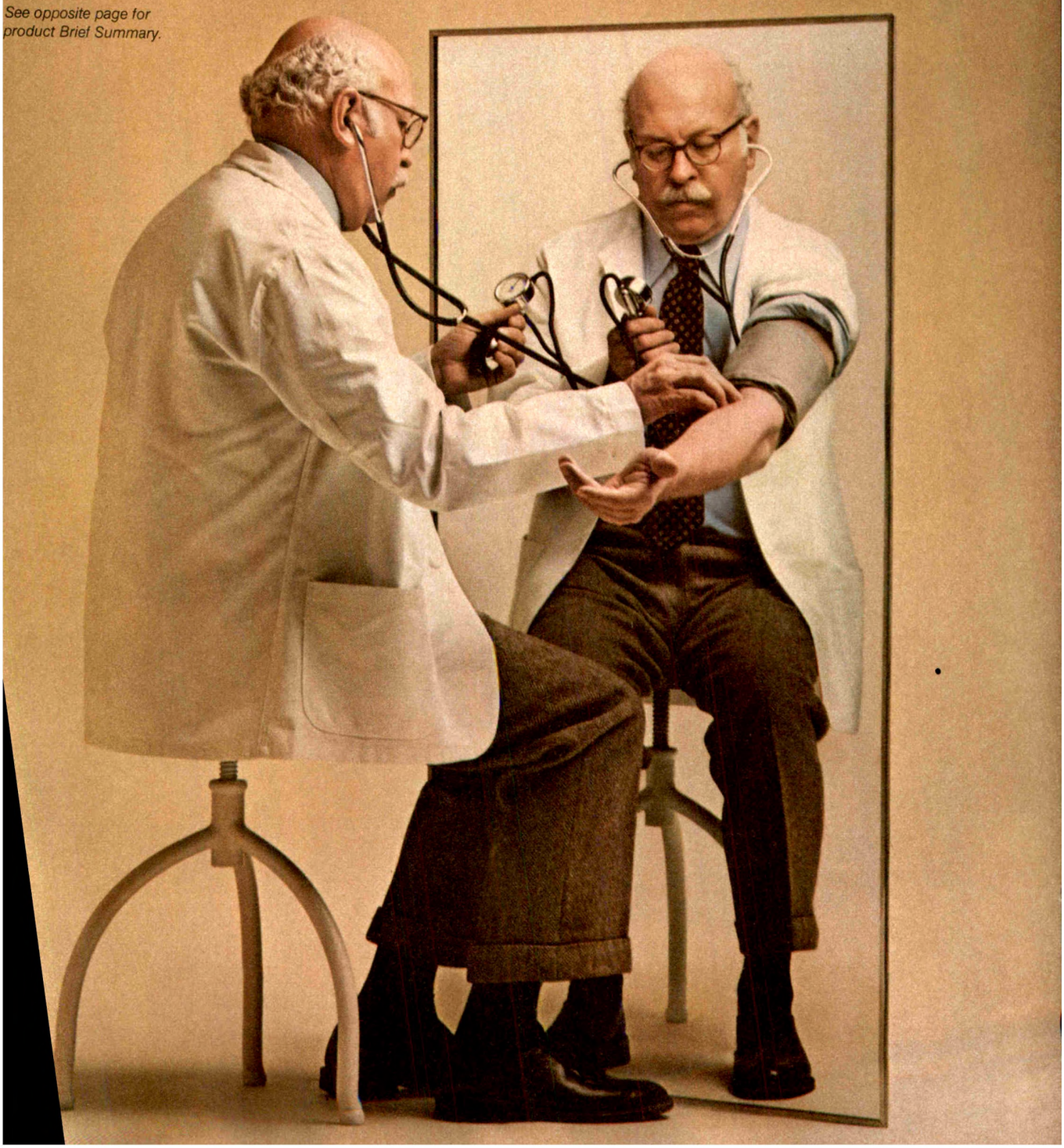
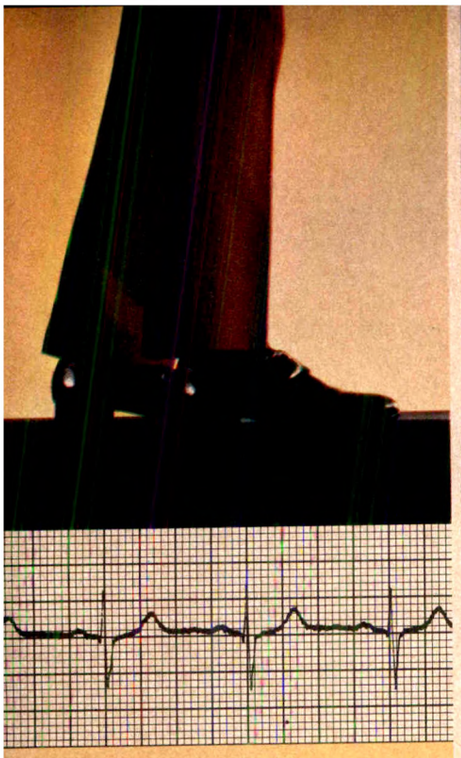
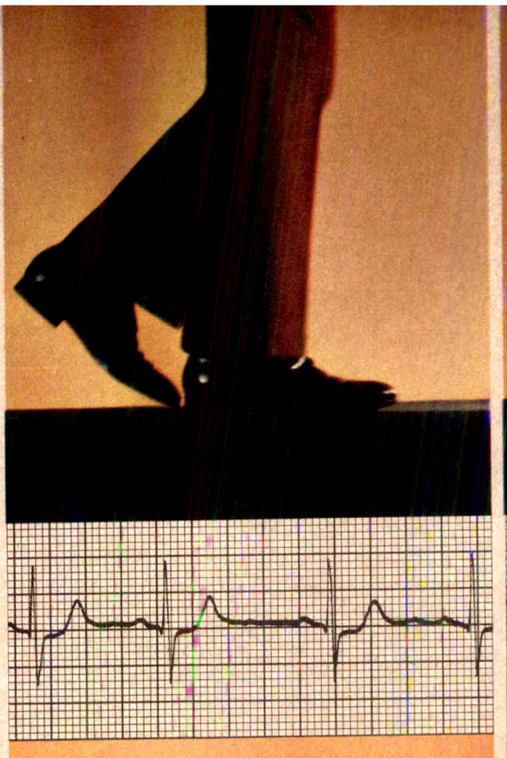
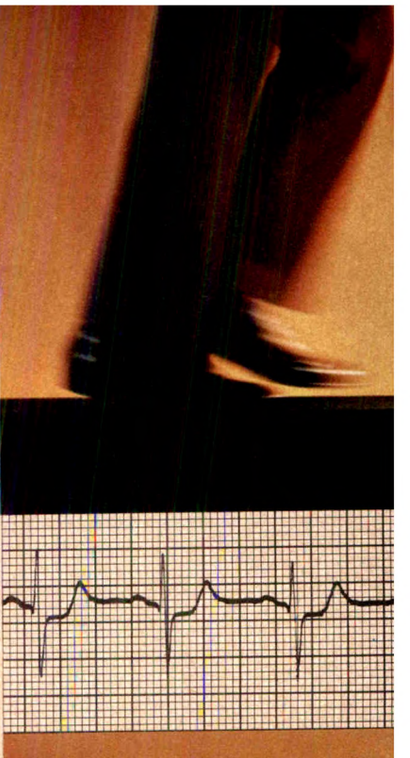




Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.



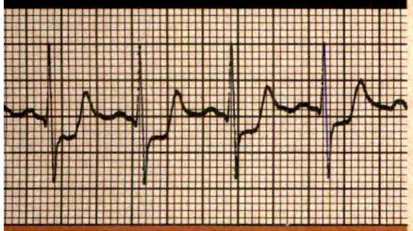
4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and impregnated foam pad which is slightly oversize to assure positive, continuous pressure at the electrode-skin surface. The results: immediate onset and virtual elimination of base line instability and motion artifact.



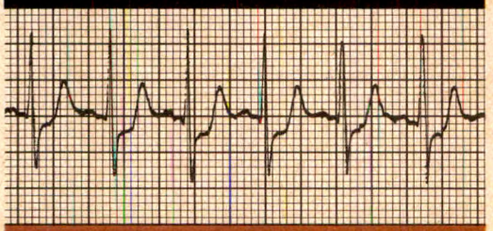
4th Minute at 3 mph (8th minute test), 0% Grade, V-5, HR-83. (T patient's ECG indicates 1 mm of depression.) Fully shielded cable and leadwire provide an effectiv barrier to the electrical interfere that might otherwise mask smal amounts of S-T depression.

Finally.

An electrode/cable system specifically designed for stress testing.

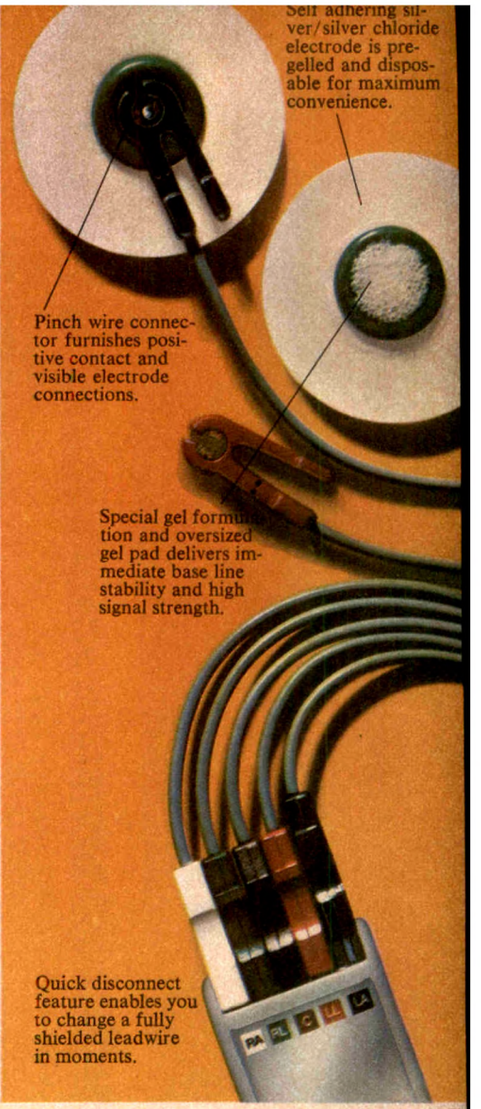


Minute at 3 mph (12th minute
est), 5% Grade, V-5, HR-117.
T depression increases to 2.5 mm.)
n at high work loads, the Ameri-
Stress Test Electrode and fully
elded cable system delivers a stable
e line and noise-free signal.



4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.)
Long test procedures* seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

* Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's new Stress Test Electrode and fully shielded cable system.

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improve exercise tolerance

reduce nitroglycerin requirements

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Persantine®

Tablets of 25 mg.

dipyridamole

the non-nitrate
coronary vasodilator

*INDICATIONS–Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS–No specific contraindications are known.

PRECAUTIONS–Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS–Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION–The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

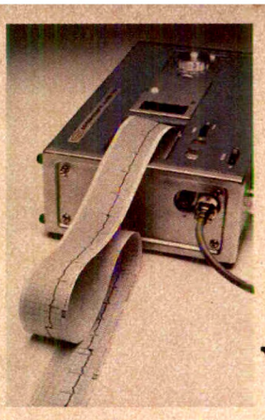
Taoist Eye-Heart Pathway
Representation of inner man as conceived by Taoism. Note the connecting line running from the eye to the heart. The eye-heart pathway may well allude to the Taoist principles of the right path delineated by Confucian philosophy—the path of virtuous conduct.

BOEHRINGER INGELHEIM

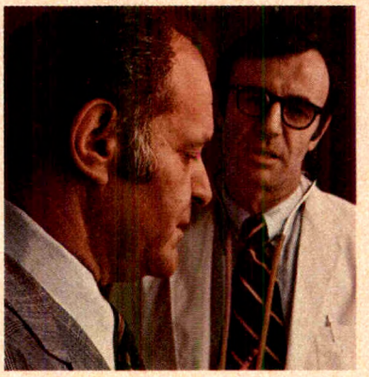
Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

A29



Why add Librium® (chlordiazepoxide HCl) to your cardiovascular regimen?

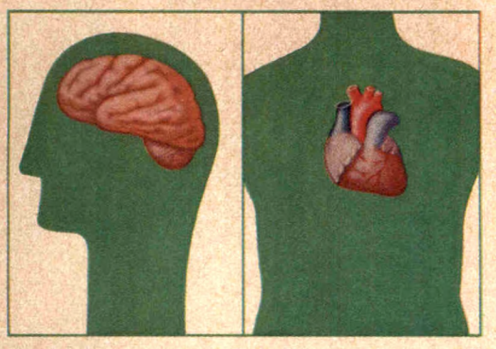


Excessive anxiety in susceptible patients can set in motion a chain of responses which add to the heart's work and thereby increase the possibility of cardiovascular complications. Furthermore, intense anxiety may interfere with effective medical management since some patients, in an attempt to deny their illness, may resist acceptance of necessary medication, dietary restrictions and other therapeutic directives. When counseling and reassurance alone are inadequate to relieve undue anxiety, adjunctive Librium (chlordiazepoxide HCl) may be beneficial.

"Specific" for anxiety reduction... wide margin of safety

Librium is used as an adjunct to primary cardiovascular medications, since it acts directly on the central nervous system, reducing excessive anxiety and emotional tension. In so doing, Librium indirectly affects cardiovascular function.

Librium has a high degree of antianxiety effectiveness with a wide margin of safety. In proper dosage, Librium usually helps calm the overanxious patient without unduly interfering with mental acuity or general performance. In the elderly and debilitated, the initial dosage is 5 mg *b.i.d.* or less to preclude ataxia or oversedation, in-



creasing gradually as needed and tolerated.

Librium is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics, antihypertensive agents, vasodilators and anticoagulants. Although clinical studies have not established a cause and effect relationship, physicians should be aware that variable effects on blood coagulation have been reported very rarely in patients receiving oral anticoagulants and Librium. After anxiety has been reduced to tolerable levels, Librium therapy should be discontinued.

For relief of excessive anxiety
adjunctive

Librium® 10 mg
(chlordiazepoxide HCl)
1 or 2 capsules t.i.d./q.i.d.

ROCHE

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

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Division of Hoffmann-La Roche Inc.
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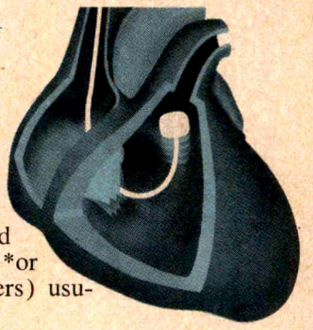
First
Fl

Balloon-Tipped Catheters



Swift access to the pulmonary artery* at bedside.

The *Swan-Ganz* Flow-Directed Catheter product line encompasses an expanding series of cardiac catheters which are directed by force of blood flow on the balloon into the pulmonary artery (*or into the right ventricle, in the case of the Bipolar Pacing Catheters) usually in one minute or less.

These catheters can provide valuable hemodynamic information to the cardiologist at bedside without requiring removal of the critically ill patient from bed to a fluoroscopy facility. Specific models are available to the pediatric cardiologist for diagnostic use in infants and children.

First with the concept, the *Swan-Ganz* catheters maintain preeminence through constant adaptation and refinement of the flow-directed principle to meet a diversity of diagnostic and therapeutic challenges. Present applications range from the ICU/CCU to the operating room and post-surgical recovery unit, anesthesiology department, pediatric section, pulmonary department, burn unit, and cardiac catheterization laboratory. Future applications of the flow-directed principle are the subject of continuing research at Edwards Laboratories.

Please write to the Vice President, Marketing, Edwards Laboratories, for *Swan-Ganz* Flow-Directed Catheter data, reprints of journal articles, and personal answers to any questions you may have. If you prefer, an Edwards Laboratories technical representative will be glad to call on you at your convenience.

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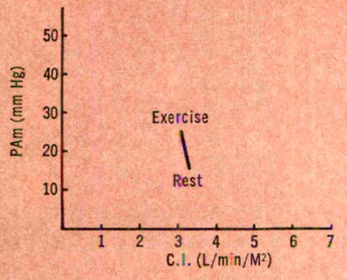
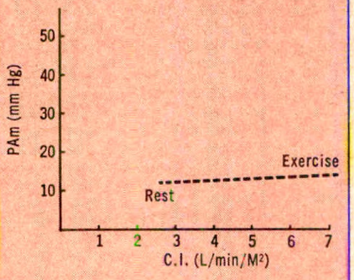
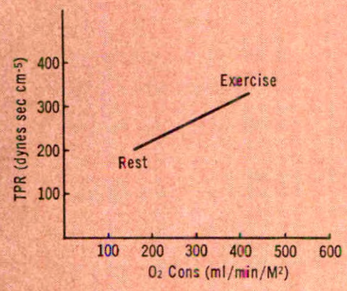
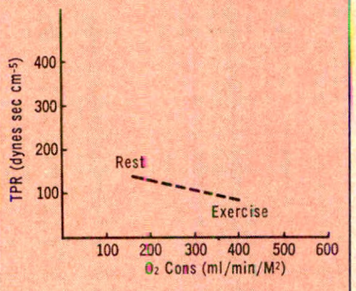
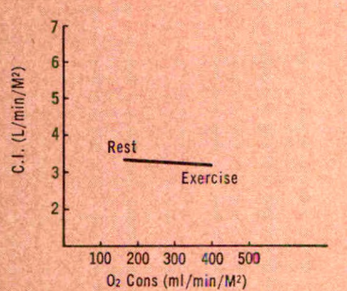
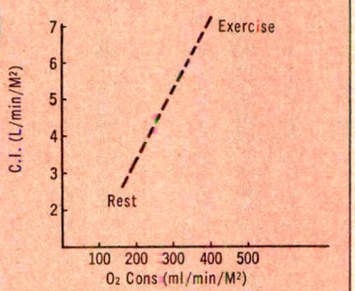
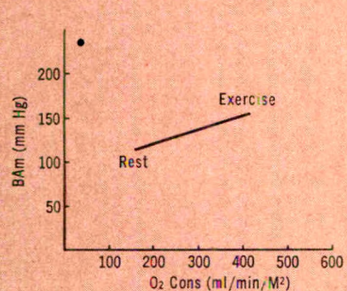
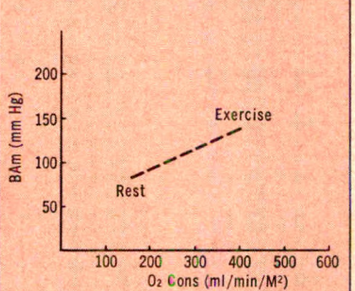
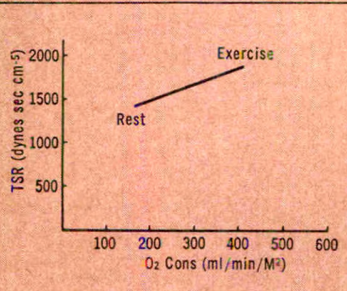
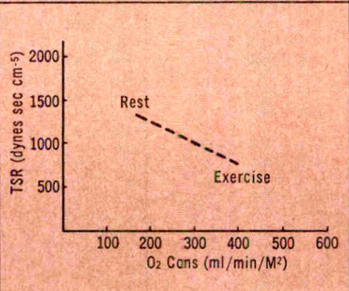
Physicians should thoroughly acquaint themselves with the procedures involved as well as cautions to be observed during insertion and manipulation of these catheter instruments.

HEMODYNAMICS OF ANGINA PECTORIS* —PATIENTS RESTING AND EXERCISING, BEFORE AND AFTER ISORDIL® SUBLINGUAL

(isosorbide dinitrate)

BEFORE MEDICATION		AFTER 5 mg. ISORDIL SUBLINGUAL (isosorbide dinitrate)
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

IN ANGINA PECTORIS*

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday stress

ISORDIL® SUBLINGUAL

(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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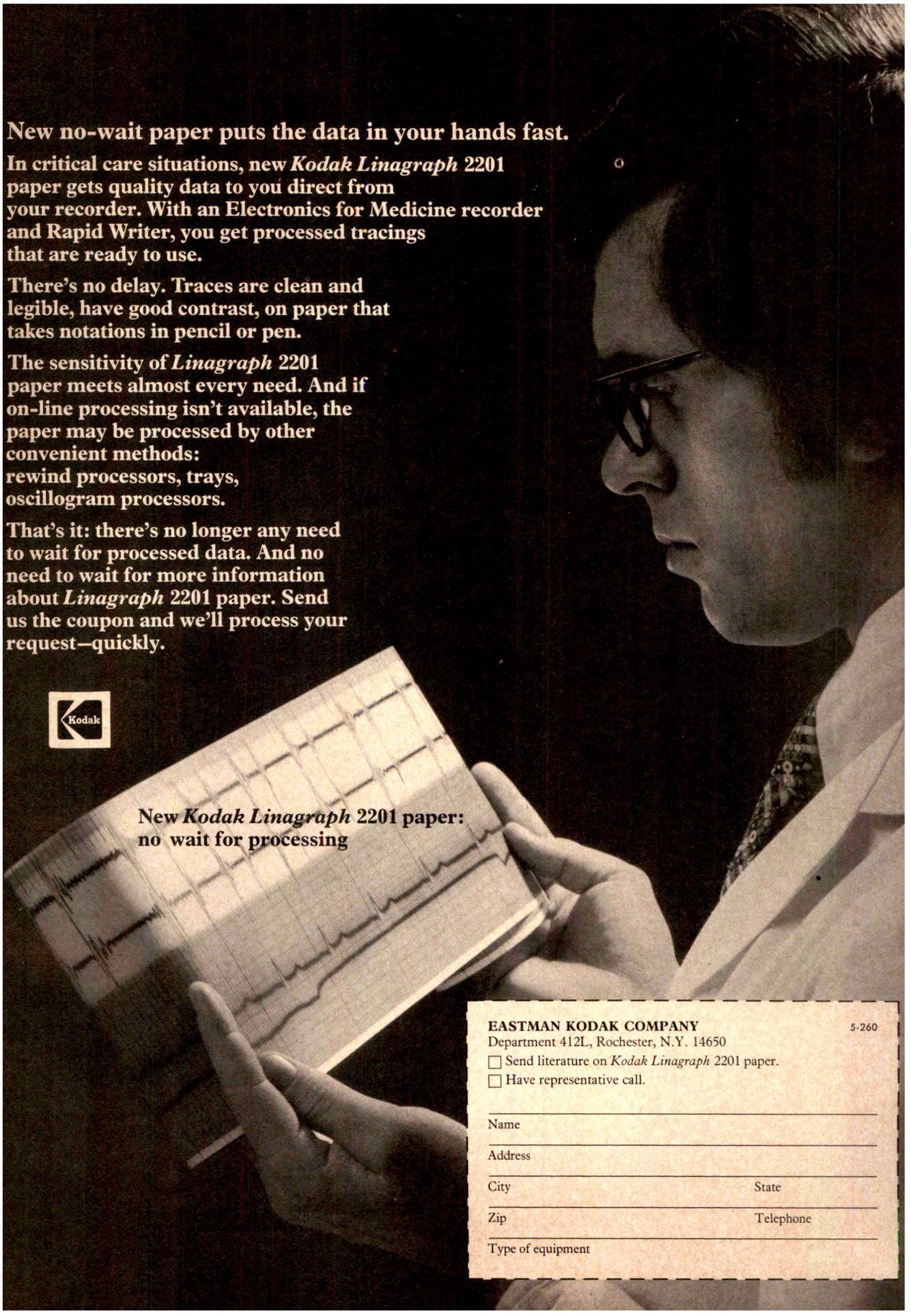
New York, N.Y. 10017

DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: * Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.



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Type of equipment

Lifeguard 1500 portable defibrillator saves you headache while saving patient's lives.

When you need a quick reaction lifesaving tool for ECG monitoring and defibrillation, you need the Lifeguard LG 1500 from Gould, the portable, battery operated defibrillator with built-in cardioscope and synchronizer for cardioversion.

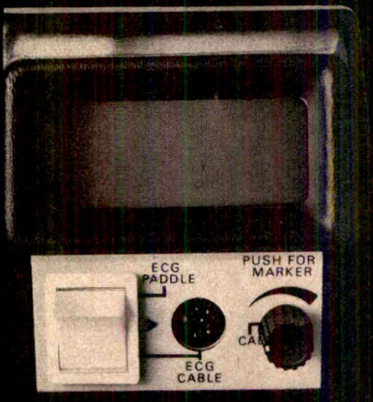
Easy to use.

Everything about the LG 1500 is designed for fast, effective action. For "quick look" or emergency monitoring, you can

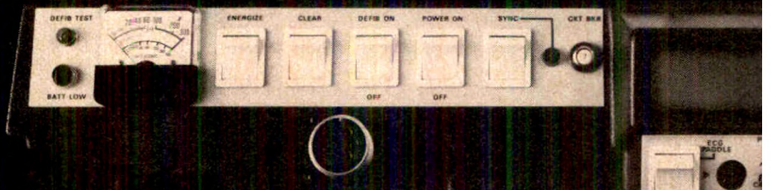
obtain the ECG signal through the paddle electrodes. Standard ECG electrodes and cables, which are stored in pockets built into the lid, may also be used.

The built-in monitoring cardioscope produces clear, readable ECG traces even in bright ambient light conditions.

The panel controls and indicators are logically located and arranged for people in a hurry. All switches are positive

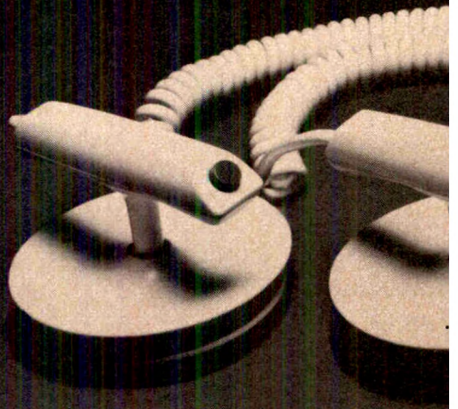


action and clearly labeled. A large, illuminated meter shows the energy level in both delivered and stored energy units. If the operator selects an energy level higher than desired, he can



simply lower it to the proper level by pressing a clear button. This also saves battery energy.

Paddles have handles lik pistol grips so the operator get a firm grip when removi paddles from their holders a pressing them against a pat chest. To give precise cont discharge timing, there is a pushbutton on each handle.



The LG 1500 is easy to carry. It's a trim, 25 pounds. Just a little larger than an attache case. The case is thin and the handle is balanced, so you can carry it naturally and easily, without straining your arm or banging it into your leg.

Outstanding safety features.

Take the paddles, for example. They have dual insulating rings

path between the handles and the electrodes. The bottom ring insulation prevents contact with the electrode and contact gel. The top ring, which is larger in diameter, is contoured so even if the operator's hand or fingers slip, they won't touch the electrodes.

The discharge control device—unique all-electronic Plasatron—eliminates circuit "ringing" due to contact bounce, which could cause deadly refibrillation. It also assures a virtually pure Lown waveform.

All high voltage circuits are isolated and the front panel controls and case are non-conductive. For maximum patient safety, the ECG input circuits are also isolated to minimize leakage to less than 10 microamps.

Chances of a premature discharge are minimized because of the location of the pushbuttons they have to be pressed simultaneously.

Superior performance and reliability.

The hermetically sealed, all-electronic Plasatron device is unexcelled for reliability. It has no moving parts and no contacts to pit, corrode, bounce or weld shut. Life expectancy is more than 100,000 operations, many times greater than electro-mechanical devices.

For maximum effectiveness, the LG 1500 provides infinitely selectable delivered energy levels from 10 to 320 watt-seconds, with up to 90 maximum-energy discharges from a fully charged battery.

An output connector permits graphic recording of ECG. It also provides an FM signal for transmitting ECG by radio or telephone.

What's more, the LG 1500 is rugged and durable. It will take rough handling, bumps and jars in stride.

Simple to service.

All the critical circuit components for the LG 1500 are on plug-in p.c. boards for quick, easy replacement.

A true value.

When you consider all you get with the LG 1500, you'll probably be pleasantly surprised at its low cost. For complete details and specifications, write today for our new, free brochure.

Write: Gould Inc., Medical Systems, 384 Santa Trinita Avenue, Sunnyvale, California 94086 or Kouterveldstraat Z/N, B 1920 Diegem, Belgium.

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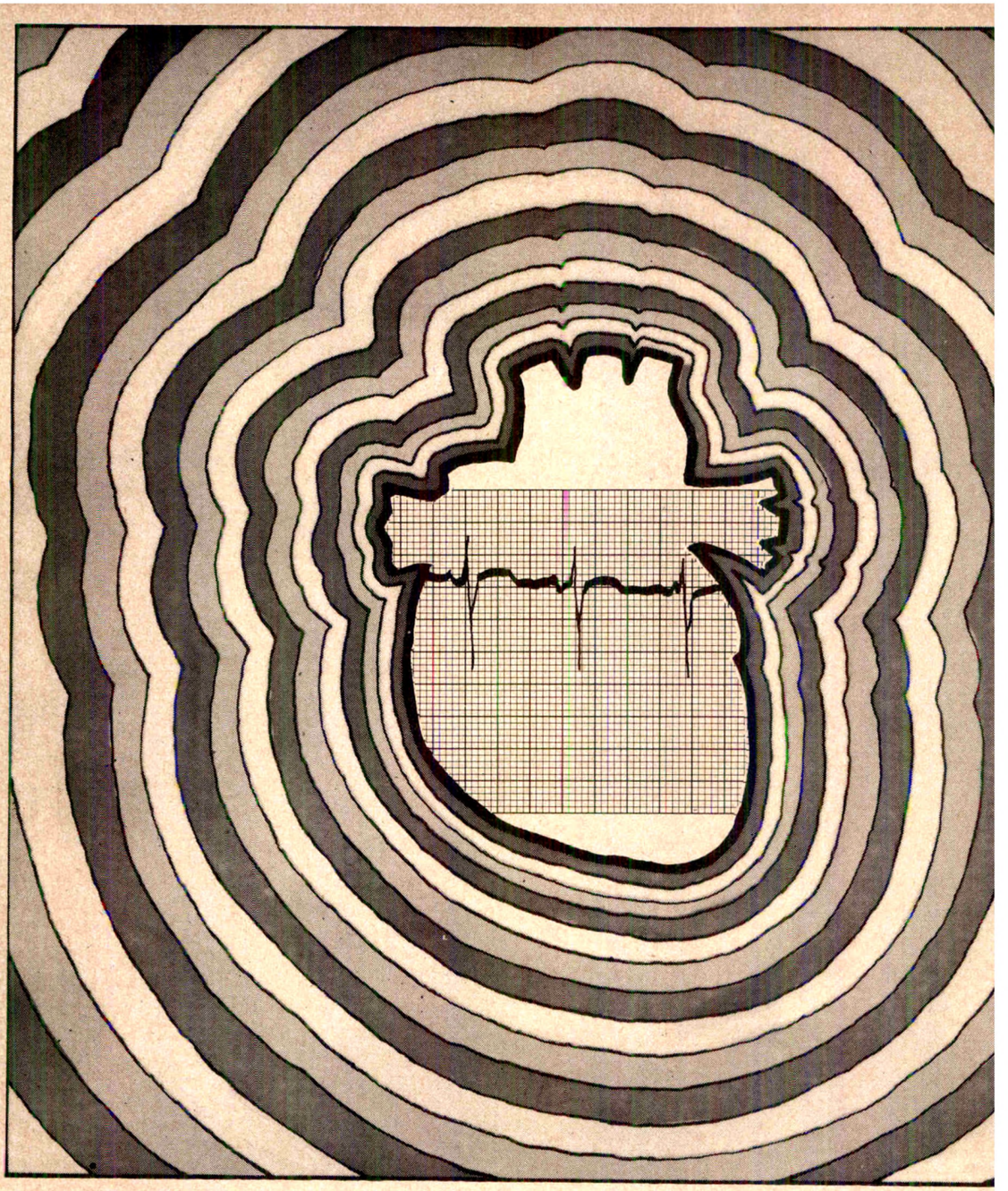

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Accurate interpretation of analytical data presented by your electrocardiograph and subsequent proper diagnosis is manifested by the chart paper.

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Thrombo embolism

The Silent Threat

"Thrombotic phenomena now occupy first place as a complicating factor, if not the cause, of mortality as determined in all autopsy series in the United States today. Thrombotic disease has become an increasingly important cause of disability and death as infectious diseases have responded to chemotherapy and as public health measures have become increasingly effective."

Contributing to the seriousness of the problem is the fact that "At present there is no satisfactory technique for the recognition in man of the incipient or active thrombotic state."[1] There are, however, a number of factors which are known to predispose to thrombus formation and potentially fatal embolism. Recognition of these factors, plus the application of adequate prophylactic and therapeutic measures, could contribute significantly toward decreasing the morbidity and mortality caused by 'the silent threat.'

The population at risk

Although such modern techniques as isotopic lung scanning, the radioactive fibrinogen uptake test, and the Doppler ultrasound flow detector show promise of permitting early detection of thrombus formation, it is generally agreed that these methods are not completely accurate as diagnostic tools, nor are they practical for large-scale patient screening. As a result, most physicians rely on the presence of known predisposing factors as a means of identifying patients who are especially prone to venous thrombosis and pulmonary emboli.

The high risk groups

As one authority has noted, these high risk "...groups include severely injured patients, particularly those over age 50 who have fractures of the pelvis, hip, or lower extremities; those undergoing elective cup arthroplasty or pelvic surgery; those immobilized or completely bedridden; those with a previous history of venous thrombosis or pulmonary embolism; those with severe obesity or congestive heart failure, or any combination of the above categories."[2]

Myocardial infarction: a special high risk category

Patients with acute myocardial infarction comprise another high risk group, especially if they have "...large transmural infarctions, previous infarction or angina, severe hypotension or shock, congestive heart failure, chronic atrial fibrillation, or past history of venous thrombosis or embolism."[2]

Therapy to lessen the risk

In patients with conditions known to predispose them to thrombosis and potentially fatal pulmonary embolism—the high risk groups—the use of anticoagulant therapy can be of significant benefit. As one investigator recently remarked: "If [the physician] believes that the risk of embolism is high he should use the only proved form of prevention, anticoagulation."[3]

With special regard to pulmonary embolism, it has been noted that "...a pulmonary infarct proves the existence of intravenous thrombosis and should be considered as a warning of possible further emboli. It is generally accepted that diagnosis of pulmonary infarction justifies the immediate application of anticoagulant therapy. Heparin is usually used initially, then oral anticoagulants (most commonly warfarin). The length of such therapy is often arbitrary, averaging four to six weeks, but depends on the extent and chronicity of the venous disease, whenever these can be determined."[4]

Myocardial infarction: a special case for longer term therapy

Following acute myocardial infarction patients are especially prone to such thromboembolic complications as mural and venous thrombosis and pulmonary and systemic emboli. The increased risk is due to reduced cardiac output, reduced arterial perfusion of the limbs, hypercoagulability (in the presence of cardiac ischemia), and venous pooling in the lower limbs—all of which may induce venous stasis leading to potentially fatal thrombus formation and embolization.

Because of the great risk of thromboembolic complications after myocardial infarction, anticoagulant therapy is widely recommended. As noted in a recent study, "...an excellent case can be made for the use of anticoagulants for the prevention of thromboembolic complications [following acute myocardial infarction]."[5]

With regard to duration of therapy, although there is no consensus, it is generally agreed that anticoagulants should be given for as long as observable benefits persist. In a study of 735 myocardial infarction patients treated with COUMADIN or another coumarin derivative: "Results indicate that anticoagulant therapy reduces the death rate significantly during the first three years after an acute myocardial infarction. However, survival rates converge after the third year, and by the fifth year there is no difference in survival of treated and untreated groups. Therapy appeared to be more effective in patients who had experienced more than one infarction. The incidence of recurrent infarction and congestive heart failure was less in the group treated with anticoagulants."[6]

Another investigator expressed his opinion on the duration of therapy by remarking that "...male patients on anticoagulants during the acute phase of myocardial infarction can logically be kept on them for 2 or 3 years when feasible. Such treatment can be recommended especially to men under age 55 and to men who have had a previous history of angina pectoris, myocardial infarction, or both, since they are the ones most likely to benefit."[2]

References:

1. Report of Inter-Society Commission for Heart Disease Resources, Sub-Committee on Thromboembolism, Wessler, S. (Chairman), *et al.*: Circulation *41*:A-31 (June) 1970.
2. Borden, C.W.: Med. Clin. North America *56*:235 (Jan.) 1972.
3. Browse, N.L.: New England J. Med. *287*:145 (July 20) 1972.
4. Selzer, A.: Medical World News: Cardiovascular Review, 1972, p. 88.
5. Ebert, R.V.: Circulation *45*:903 (April) 1972.
6. Ebert, R.V., *et al.*: JAMA *207*:2263 (Mar.) 1969.

COUMADIN®
(crystalline sodium warfarin*)

*present as crystalline sodium warfarin isopropanol clathrate

Please refer to brief summary of prescribing information on last page of this advertisement.

COUMADIN (crystalline sodium warfarin) BRIEF SUMMARY

EFFECTIVENESS: Coumadin® (crystalline sodium warfarin) is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

CONTRAINDICATIONS: Hemorrhagic blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms—cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities,** or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional block anesthesia.

WARNINGS: Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risk of hemorrhage due to anticoagulants is weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with increased risk of hemorrhage: **Pregnancy**—oral anticoagulants pass through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage *in utero*, even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. **Lactation**—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Severe trauma** of head, bones or muscles associated with extreme raw surfaces. **Surgery** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS: Periodic determination of prothrombin time is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinal; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; Coumadin® (crystalline sodium warfarin) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm./day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; Coumadin® (crystalline sodium warfarin) underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to Coumadin. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

ADVERSE REACTIONS: Potential side effects of Coumadin® (crystalline sodium warfarin) include: 1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.) Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc. 2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

TREATMENT FOR OVERDOSAGE: Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing Coumadin® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of Coumadin® (crystalline sodium warfarin) may suffice; and if necessary, small doses of vitamin K_1 (Mephyton®*) orally, 2.5 mg., will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 (AquaMephyton®*) in doses of 10 to 25 mg. may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.) Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of Coumadin® (crystalline sodium warfarin) administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level is readily obtained.

*Trademark, Merck Sharp & Dohme.

For complete prescribing information, including dosage and laboratory control, see package circular.

SUPPLIED: Tablets: Coumadin® (crystalline sodium warfarin) for oral use, single scored, imprinted numerically with potency as follows: 2 mg. lavender, 2½ mg. orange, 5 mg. peach, 7½ mg. yellow, 10 mg. white, 25 mg. red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100. **Injection:** Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units, 50 mg.: Unit consists of 1 vial, 50 mg.; sodium chloride, 10 mg.; thimerosal, 0.2 mg. accompanied by a 2 ml. ampul Sterile Water for Injection. 75 mg.: Unit consists of 1 vial, 75 mg.; sodium chloride, 15 mg.; thimerosal, 0.3 mg. accompanied by a 3 ml. ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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Physician and Patient Aids Available on Request—record charts for you, dosage calendars and instruction folders, including identification cards, for your patients. For a free supply of any or all of these aids, ask your Endo representative or write to Director of Professional Services.

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*present as crystalline sodium warfarin isopropanol clathrate

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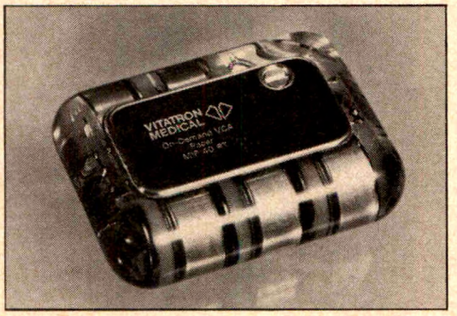
100% Pacemaker Analysability: Vitatron Medical



The present generation Vitatron Medical pacemakers are completely analysable during implantation.

The digital pacemaker analyzer MPA 1 allows post-operative determination of all important pacemaker parameters such as electrode impedance in ohms and stimulation threshold in mA.

A regular review of the data will determine the run down of a pacemaker's lifetime well in advance.

Use of Vitatron Medical VCA pacemakers eliminates the need for elective pacemaker replacement.

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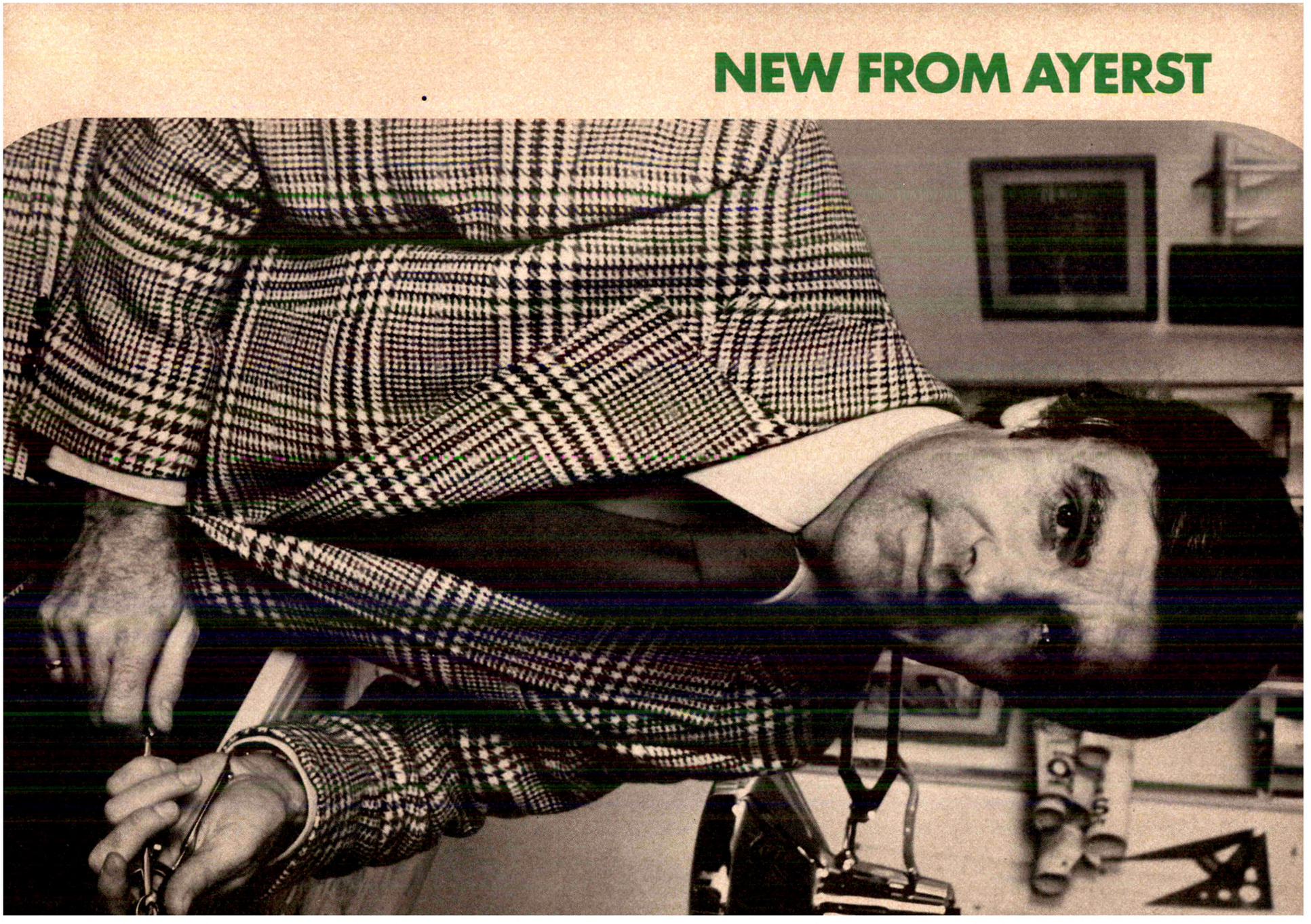
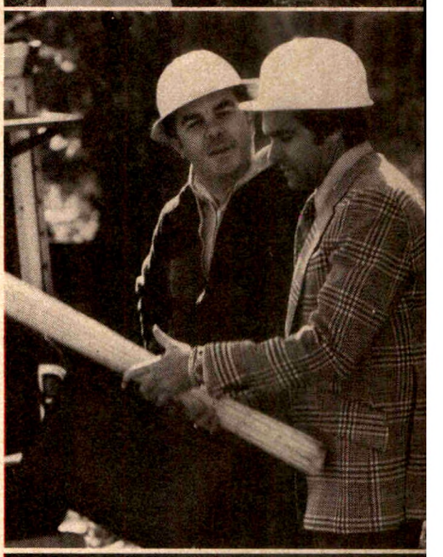


the "healthy" hypertensive



It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

DIUCARDIN provides approximately the same diuretic potency as hydrochlorothiazide at maximal therapeutic dosage. With DIUCARDIN, the onset of diuresis is gradual and may be maintained for twelve hours or more with a single dose.[1,2] The antihypertensive effect of DIUCARDIN is usually maintained in long term use. For many patients on DIUCARDIN, a convenient once-a-day dosage may suffice.

Based on efficacy *and* economy, DIUCARDIN provides a good beginning for many hypertensive patients. New DIUCARDIN 50 mg. Tablets. For mild to moderate hypertension and adjunctive therapy for many types of edema. Ayerst®

controlled early on

Diucardin® TABLETS

(hydroflumethiazide)

diuretic/antihypertensive

(See prescribing information on next page.)

NEW FROM AYERST

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

diuretic/antihypertensive

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: Hypertension: DIUCARDIN alone may provide adequate control in mild or moderate hypertension. In severe hypertension or in cases of mild or moderate hypertension which do not respond adequately, DIUCARDIN may be used in conjunction with other antihypertensive agents.

DIUCARDIN alone or in conjunction with other antihypertensive agents is indicated for control of hypertension in pregnancy. (See WARNINGS)

Edema: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

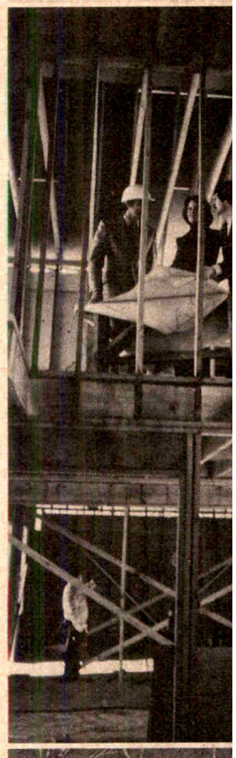
Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: Usual adult dosage: 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN—No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.



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Make Life Easier For You And Your Pacer Patients

Now, with the advent of the ESB Medcor Pacer-Check* system, it is possible for your office to conduct regular, accurate recordings of heart pacer patient's ECG and pacer rates by telephone.

Both you and your patients benefit. Now, with no more than a phone call, you can have information which permits elective decisions on replacement rather than emergency or prophylactic replacements. (By using a regular patient checking program, maximum pacer life can be realized.) Your patient and you have flexibility and safety at the same time.

This two-component system operates simply, requiring minimal training to both your personnel and patients.

The Medic Unit, at left, is the central component and is usually located in the hospital or clinic. It receives ECG and pacer rate input via unaltered telephones from the Patient Unit which is usually located in the patient's home. ECG data, produced on a standard paper chart, indicates the relationship between the QRS complex and pacer artifact to ascertain pacer capture. Pacer rate is shown continuously by illuminated numbers on the front panel. This is the first system available to physicians that records ECG and simultaneously displays pacer rate.

The Patient Unit is lightweight and battery powered. It is capable of transmitting from any telephone to your office. Transmissions have been successfully made from such great distances as Tokyo to New York. To operate, the patient places the telephone headset in the receiving cradle and then slips the two expandable bracelets over his forearms. Transmission begins immediately.

The Pacer-Check* system, approved for reimbursement by Medicare, has proven itself a useful and self-supporting method of maintaining a desirable pacer program.

If the unique qualities of the Pacer-Check* system interest you, contact ESB Medcor, Inc., Dept. 373, 5920 Rodman St., Hollywood, Florida 33023. Toll free call: (800) 327-9780, Ext. 373.

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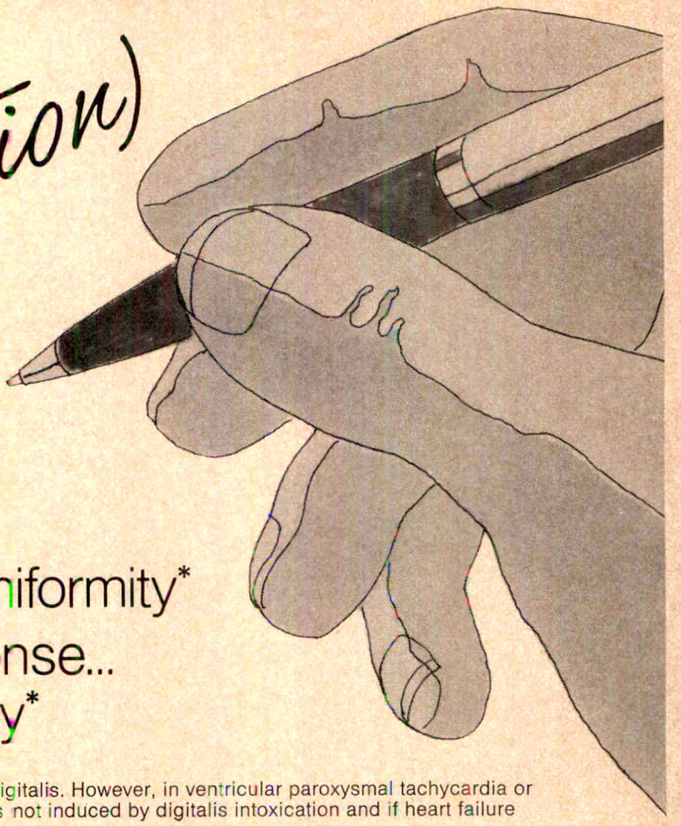

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precision quality control...

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Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

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MAY 6, 1974

The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 5

CLINICAL STUDIES

Bundle Branch Block

Demonstration of the Incomplete Nature of Some "Complete" Bundle Branch and Fascicular Blocks by the Extrastimulus Technique

DELON WU, MD
PABLO DENES, MD
RAMESH DHINGRA, MD
KENNETH M. ROSEN, MD, FACC

Chicago, Illinois

The incomplete nature of some electrocardiographic "complete" bundle branch and fascicular blocks is demonstrated using the atrial extrastimulus technique. Patient 1, with a QRS pattern of "complete" left bundle branch block, manifested a QRS pattern of right bundle branch block at a shorter coupling interval, indicating that the left bundle could conduct. Patient 2, with a QRS pattern of right bundle branch block and "complete" left anterior hemiblock, manifested a pattern of left posterior hemiblock at a shorter coupling interval, indicating that the left anterior fascicle could conduct. Patient 3, with a normal QRS complex, showed left bundle branch block at shorter coupling intervals and then a pattern of right bundle branch block as the coupling interval was further decreased, indicating that functional left bundle branch block was incomplete. This demonstration of partial bundle branch block depends on a discordance of conduction time and refractory period, the bundle or fascicle with depressed conduction (incomplete block) having a shorter refractory period than the more normally conducting bundle or fascicle. This discordance may be related to the development of trifascicular block in patients with bifascicular block and a normal H–V interval. It is a predisposing factor in the complex patterns of aberrant conduction seen during supraventricular tachyarrhythmias with varying cycle lengths.

It has been suggested that a critical degree of slowing in a bundle branch or fascicle could produce the electrocardiographic pattern of "complete" bundle branch or fascicular block.[1–3] The incomplete nature of such complete block is not apparent on the surface electrocardiogram. In this study, we were able to demonstrate the incomplete nature of some complete bundle branch and fascicular blocks using the extrastimulus technique. This demonstration is dependent upon a discordance of conduction time and refractory period in portions of the His-Purkinje system in these patients, the bundle branch or fascicle with depressed conduction (incomplete block) having a shorter refractory period than the remaining more normally conducting portions.

This discordance of conduction time and refractory periods may also be related to the development of complete block in patients with bifascicular block and a normal H–V interval, and to the understanding of the complex patterns of aberrant conduction seen during supraventricular tachyarrhythmias with varying cycle lengths.

From the Section of Cardiology, Department of Medicine, Abraham Lincoln School of Medicine of the University of Illinois College of Medicine, and the West Side Veterans Administration Hospital, Chicago, Ill. This work was supported in part by National Institutes of Health Contract 71-2478 under the Myocardial Infarction Program, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md., and by Basic Institutional Support, West Side Veterans Administration Hospital, Chicago, Ill. Manuscript accepted October 4, 1973.

Address for reprints: Kenneth M. Rosen, MD, Section of Cardiology, University of Illinois College of Medicine, 840 S. Wood St., Chicago, Ill. 60612.

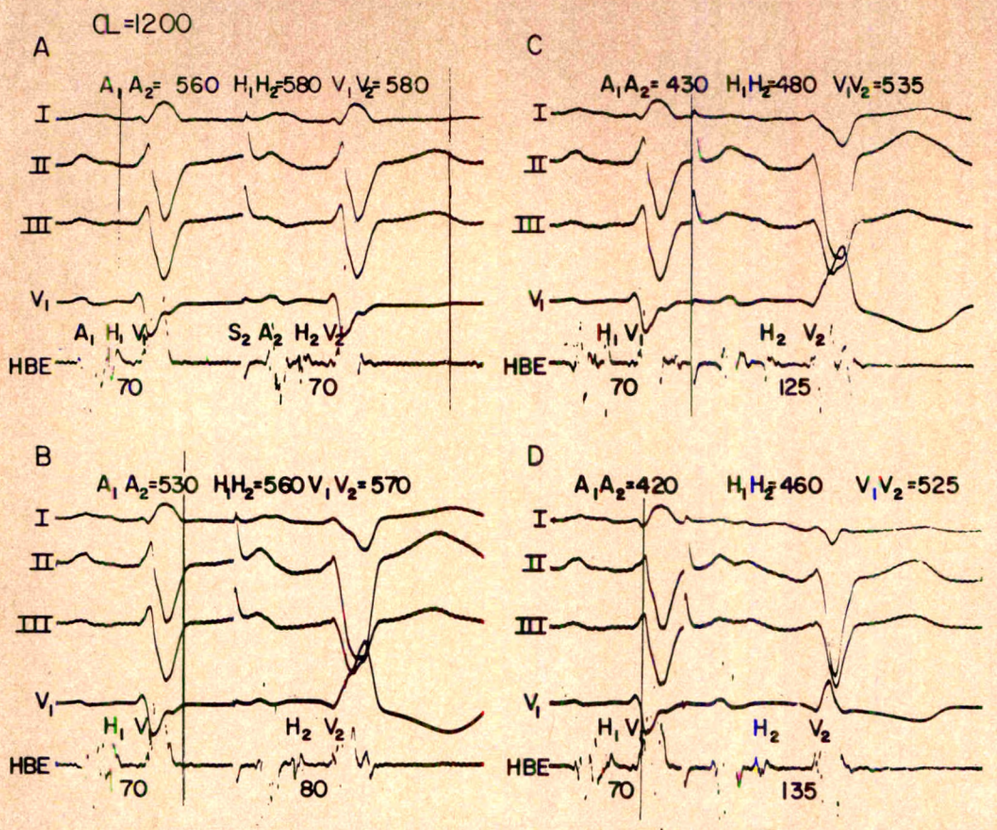

FIGURE 1. Case 1. Demonstration of the incomplete nature of "complete" left bundle branch block. Shown are electrocardiographic leads I, II, III and V_1 and a His bundle electrogram (HBE). A_1, H_1, V_1, S_2, A_2 and V_2 are labeled. A_1–A_2, H_1–H_2 and V_1–V_2 intervals are listed at the top of each panel. H_1–V_1 and H_2–V_2 intervals are listed at the bottom of each panel. Each panel shows the last of 10 sinus beats (cycle length [CL] 1,200 msec) and the extrastimulus and its responses at A_1–A_2 intervals of 560 msec **(A)**, 530 msec **(B)**, 430 msec **(C)** and 420 msec **(D)**. The coupled QRS complex has a pattern of left bundle branch block in **A** and a pattern of right bundle branch block in **B, C** and **D.** (See text for discussion.) Paper speed is 100 mm/sec and time lines are at 1 second intervals in this and all subsequent illustrations.

Methods

Electrophysiologic studies were performed in three patients in the supine, postabsorptive, nonsedated state. Informed consent was obtained from all patients. His bundle electrograms were recorded as previously described,[4] using a tripolar electrode catheter percutaneously introduced into a right femoral vein. A second quadripolar electrode catheter was percutaneously introduced into the left femoral vein and positioned in the high right atrium. The distal two electrodes of the quadripolar catheter were used for atrial pacing and the proximal two electrodes were used for recording the right atrial electrograms. Electrocardiographic leads I, II, III and V_1 and high right atrial and His bundle electrograms were recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. The electrical stimuli were provided by a digital programmable pulse generator (constructed by M. Bloom, Philadelphia, Pa.).

Conduction intervals were recorded during sinus rhythm. The atria were paced at a rate slightly higher than the sinus rate and then at increasing rates (in steps of 10 beats/min) until 1:1 conduction was lost and second degree atrioventricular (A–V) block was observed. Refractory periods were measured with the extrastimulus technique.[5] The test stimulus (S_2) was introduced after every 10th driven or spontaneous sinus beat (S_1). The S_1–S_2 interval was decreased in increments of 5 to 20 msec.

Definitions

A_1, H_1 and V_1 were, respectively, the atrial, His bundle and ventricular electrograms of driven or spontaneous sinus beats; A_2, H_2 and V_2 were the atrial, His bundle and ventricular responses to the test stimulus. A–H, H–V, H_1–H_2 and V_1–V_2 intervals were defined and measured as described by Wit et al.[5] The relative refractory period of the ventricular specialized conduction system was defined as the longest H_1–H_2 interval at which H_2 was conducted to the ventricle with lengthening of the H_2–V_2 interval relative to the H_1–V_1 interval of driven or spontaneous beats. The effective refractory period of the ventricular specialized conduction system was defined as the longest H_1–H_2 interval at which H_2 failed to propagate to the ventricles. The refractory period of a bundle branch or a fascicle was defined as the longest H_1–H_2 interval at which H_2 was conducted to the ventricles with the appropriate electrocardiographic QRS pattern of either bundle branch or fascicular block. This refractory period can reflect either a relative or an effective refractory period in the particular bundle or fascicle since the extrastimulus can provoke either incomplete or complete block.

Incomplete block in a fascicle or bundle refers to slow conduction in either structure. With a critical amount of delay, this incomplete block can produce the electrocardiographic manifestations of complete block. Thus, so-called complete block may or may not reflect total interruption of conduction in a bundle branch or fascicle. Functional bun-

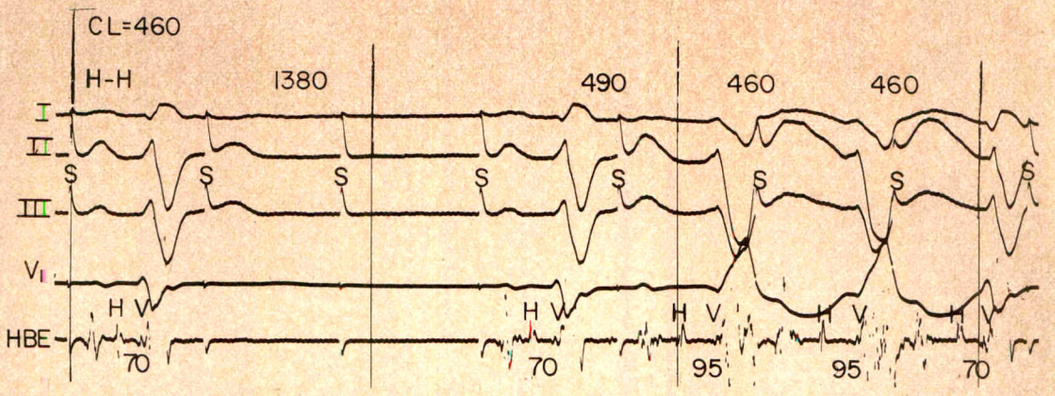

FIGURE 2. Case 1. Record showing a pattern of right bundle branch block after a long H–H interval. The atria were paced at a cycle length of 460 msec. H–H cycle lengths are listed on top and H–V intervals on bottom. The basic QRS configuration indicated left bundle branch block. The second and third beats after a long H–H interval (due to atrial noncapture) are conducted to the ventricles with a pattern of complete right bundle branch block and slight lengthening of the H–V interval from 70 to 95 msec.

dle branch block,[6] refers to the bundle branch block (aberrant conduction) produced by an extrastimulus. Again, this functional block could reflect either slowing or total interruption of conduction.

Results

Case 1

The patient was a 51 year old man with angina pectoris and congestive heart failure. The electrocardiogram showed first degree A–V block (P–R interval 210 msec), left atrial hypertrophy and complete left bundle branch block (QRS interval 170 msec, axis −60°). Electrophysiologic studies were performed during diagnostic cardiac catheterization. Recordings during sinus rhythm revealed a heart rate of 50 beats/min, an A–H interval of 95 msec and an H–V interval of 70 msec. Type I block proximal to the His bundle was noted at a paced heart rate of 170 beats/min. Premature test atrial stimuli were coupled to sinus rhythm (cycle length 1,200 msec) (Fig. 1). At initial coupling intervals, H_2 was conducted with a pattern of complete left bundle branch block (Fig. 1A). As the A_1–A_2 interval was decreased to 530 msec or less with a corresponding H_1–H_2 interval of 560 msec or less, H_2 was conducted to the ventricles with a pattern of right bundle branch block. The QRS axis was also shifted leftward to −120° and the H_2–V_2 interval was lengthened (80 to 125 msec) (Fig. 1, B and C). As the A_1–A_2 interval was decreased to 420 msec with a corresponding H_1–H_2 interval of 460 msec, H_2 was conducted to the ventricles with further prolongation of the H_2–V_2 interval (135 msec), and the QRS axis was shifted slightly rightward to −90°. The QRS configuration still indicated right bundle branch block but was narrower (Fig. 1D). Conduction was limited by an atrial effective refractory period of 370 msec. Figure 2 illustrates atrial pacing at a cycle length of 460 msec. Intermittent atrial noncapture was seen. After a long H–H interval due to noncapture, two consecutive beats were conducted to the ventricles with a pattern of right bundle branch block associated with lengthening of the H–V interval.

Comment: The results of this study indicate that the block in the left bundle branch with an electrocardiographic pattern of complete left bundle branch block was probably incomplete. This was shown by demonstration of right bundle branch block with coupled pacing, indicating that the left bundle branch could conduct. If the left bundle branch were totally blocked, superimposition of right bundle branch block with coupled pacing would produce complete block distal to the His bundle on the coupled beat. Left bundle branch block during sinus rhythm therefore reflected first degree left bundle branch block. H–V prolongation during sinus rhythm probably reflected lesser degrees of delay in the right bundle branch.

Despite a longer conduction time in the left bundle branch (incomplete left bundle branch block), the refractory period of the right bundle branch during sinus rhythm was longer than that of the left, demonstrating a discordance of conduction time and refractory period. The bundle branch with the longer conduction time (left) had a shorter refractory period than the bundle with faster conduction time (right). A pattern of right bundle branch block was also seen as the refractory period of the right bundle was lengthened after a long H–H interval due to atrial noncapture.[6,7] The shift in axis during early premature stimulation suggests an asynchronous conduction delay between the anterior and posterior fascicles. The narrowing of the QRS configuration during early premature stimulation also suggests that the functional block in the right bundle might have been incomplete.

Case 2

The patient, a 53 year old man, had angina pectoris, mild congestive heart failure and a history of previous myocardial infarction. The electrocardiogram revealed a sinus rate of 71 beats/min, a P–R interval of 160 msec, a QRS duration of 170 msec and a QRS axis of −80°. The QRS pattern was that of right bundle branch block with left anterior hemiblock and old anteroseptal myocardial infarction.

Electrophysiologic studies during sinus rhythm revealed an A–H of 89 msec and an H–V interval of 46 msec. Wenckebach phenomena above the His bundle occurred at a paced rate of 190/min. Atrial extrastimuli were coupled to spontaneous sinus rhythm (cycle length 848 msec) (Fig. 3). At an A_1–A_2 interval of 330 msec, H_2 was conducted to the ventricles with an H_1–H_2 interval of 420 msec without change in the QRS or H_2–V_2 interval (Fig. 3A). As the A_1–

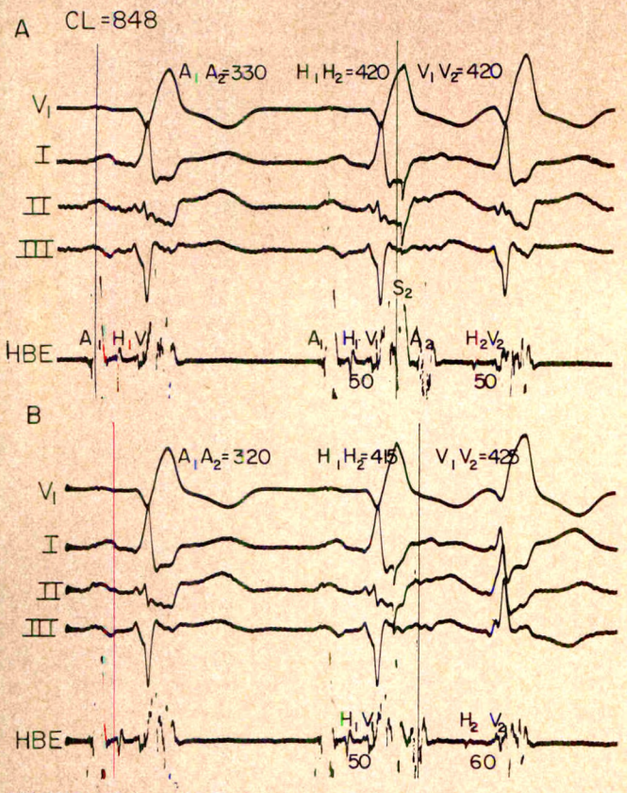

FIGURE 3. Case 2. Records showing the incomplete nature of complete left anterior hemiblock. In **A** and **B** the basic sinus cycle length is 848 msec, and the QRS pattern shows apparent complete right bundle branch block. The axis is −80°. The A_1–H_1 interval is 90 msec and the H_1–V_1 interval 50 msec. A sudden shift in the QRS axis from −80° to +120° (left posterior hemiblock) associated with lengthening of the H_2–V_2 interval from 50 to 60 msec occurs at H_1–H_2 intervals of 415 msec (third beat in **B**).

A_2 interval was decreased to 320 msec, the H_1–H_2 interval decreased to 415 msec with slight prolongation of the H_2–V_2 interval and a marked rightward shift in the QRS axis from −80° to +120° (left posterior hemiblock); the right bundle branch block pattern was unchanged (Fig. 3B). Similar results were observed in all H_1–H_2 intervals of less than 415 msec. The atrial effective refractory period of 220 msec limited A–V conduction. At a shorter driven cycle length of 610 msec, H_2 conducted to the ventricles without change in the QRS axis at all H_1–H_2 intervals (functional refractory period of the A–V node 390 msec).

Comment: In this patient, electrocardiograms showed complete right bundle branch block with complete left anterior hemiblock.[2] As the H_1–H_2 intervals were decreased to 415 msec or less, the pattern of left anterior hemiblock was replaced with a pattern of left posterior hemiblock. This change suggests that the left anterior hemiblock was incomplete since a pattern of left posterior hemiblock cannot be seen without conduction in the anterior fascicle. H_2–V_2 prolongation at close coupling intervals probably reflected slight delays in the anterior fascicle. A discordance of conduction time and refractory period is seen in this case also. The anterior fascicle had a longer conduction time but a shorter refractory period than the posterior fascicle during sinus rhythm. The refractory period of the posterior fascicle shortened with decreasing cycle length.[6,7] Right bundle branch block was probably total in this patient.

Case 3

The patient was a 68 year old man with a history of dizziness. Electrocardiograms revealed sinus bradycardia (rate 50/min) and a normal P–R interval, QRS duration and axis. Electrophysiologic studies during sinus rhythm revealed an A–H interval of 80 msec and an H–V interval of 40 msec. Wenckebach periods proximal to the His bundle were observed at a pacing heart rate of 180/min. Atrial extrastimuli were delivered at driving cycle lengths of 1,000, 640 and 480 msec.

With a cycle length of 1,000 msec, the A_1–H_1 interval was 95 msec and the H_1–V_1 interval 40 msec. At an A_1–A_2 interval of 500 msec, the H_1–H_2 interval was 530 msec, and H_2 was conducted to the ventricles with an H_2–V_2 interval of 40 msec and a normal QRS configuration. At an A_1–A_2 interval of 485 msec with a corresponding H_1–H_2 interval of 510 msec, H_2 was conducted with a pattern of left bundle branch block with a QRS duration of 125 msec; the H_2–V_2 interval remained unchanged. Similar results occurred at A_1–A_2 intervals of 485 to 440 msec with corresponding H_1–H_2 intervals of 510 to 495 msec. With A_1–A_2 intervals of 420 msec or less and corresponding H_1–H_2 intervals of 475 msec or less, H_2 was propagated to the ventricles with a QRS pattern of right bundle branch block and marked prolongation of the H_2–V_2 interval. The atrial effective refractory period of 350 msec limited A–V conduction. The rela-

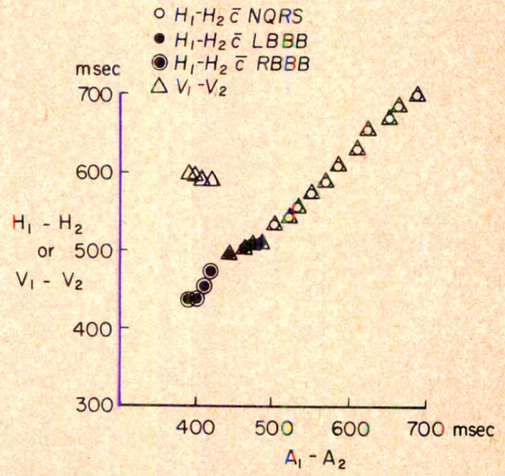

FIGURE 4. Case 3. Atrioventricular conduction curve showing development of functional left and then right bundle branch block and the relation of H_1–H_2, V_1–V_2 intervals to A_1–A_2 intervals. The driving cycle length was 1,000 msec. A_1–A_2 intervals are on the abscissa, V_1–V_2 intervals **(triangles)** and H_1–H_2 intervals **(circles)** are on the ordinate. The **open circles** indicate the H_1–H_2 intervals at which H_2 was conducted to ventricles with a normal QRS complex (NQRS); the **solid circles** indicate the H_1–H_2 intervals at which H_2 was conducted to the ventricles with a QRS pattern of left bundle branch block (LBBB); the **solid circles with a halo** indicate the H_1–H_2 intervals at which H_2 was conducted to the ventricles with a QRS pattern of right bundle branch block (RBBB). The V_1–V_2 intervals are suddenly lengthened at H_1–H_2 intervals of 475 msec or less when the QRS pattern shifts from left to right bundle branch block. (See text for discussion.)

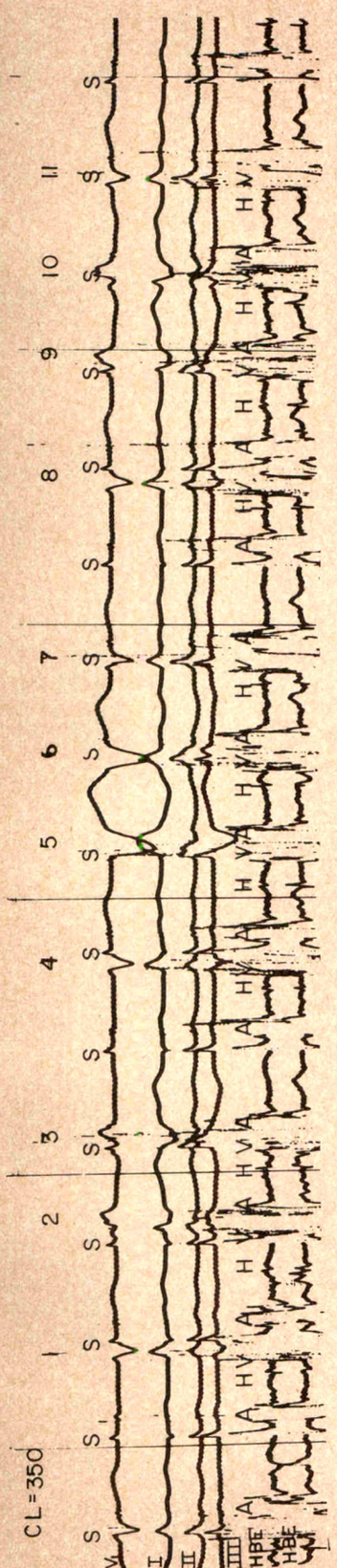

FIGURE 5. Case 3. Record showing rhythmic repetitive ventricular aberrations of both left and right bundle branch block patterns. The atria were paced at a constant interval of 350 msec; 5:4 and 4:3 Wenckebach sequences proximal to the His bundle are seen. The A–H, H–V and H–H intervals of each beat are labeled on the bottom. Beats 1, 4 and 8 are the first conducted beats with normal QRS configurations; beats 2, 5 and 9 are the second and beats 3, 6 and 10 the third conducted beats propagated with ventricular aberrations; beats 7 and 11 are the fourth conducted beats propagated to the ventricle normally. Beats 2, 3, 9 and 10 showed a pattern of right bundle branch block; beats 5 and 6 showed a pattern of left bundle branch block. (See text for discussion.)

tions are graphically demonstrated in Figure 4. The H_1–H_2 interval of 510 msec is the refractory period of the left bundle branch, and the H_1–H_2 interval of 475 msec is the refractory period of the right bundle branch. Left bundle branch block was partial as demonstrated by development of right bundle branch block with a prolonged H_2–V_2 interval (jump in the V_1–V_2 curve).

When the heart was driven at a cycle length of 640 msec, left bundle branch block occurred at an A_1–A_2 interval of 380 msec or less, and right bundle branch block was not noted. When the heart was driven at a cycle length of 480 msec, functional bundle branch block was no longer observed.

Figure 5 is a record obtained at an atrial paced rate of 180/min. Both 5:4 and 4:3 Wenckebach periods above the His bundle were noted. QRS complexes 1, 4 and 8 are the first, 2, 5 and 9 the second, 3, 6 and 10 the third and 7 and 11 the fourth conducted beats in the consecutive Wenckebach sequences. The first beat of each sequence and the fourth beat of the second and the third sequences were conducted normally (QRS complexes 1, 4, 7, 8 and 11). The second and the third conducted beats of each sequence were propagated with aberrant conduction of either left or right bundle branch block pattern associated with lengthening of the H–V intervals (QRS complexes 2, 3, 5, 6, 9 and 10). The H–V interval of the second conducted beats was always longer than that of the third conducted beat in each sequence. For those beats showing left bundle branch block aberrancy, the QRS duration of the second conducted beats was greater than that of the third conducted beats (complexes 5 and 6). For those beats showing right bundle branch block aberrancy, the QRS duration of the third conducted beats was slightly greater than that of the second conducted beats (complexes 2 and 3 and complexes 9 and 10). Aberrancy of a right bundle branch block pattern occurred more frequently than that of a left bundle branch block pattern.

Comment: The refractory period of the left bundle branch was longer than that of the right bundle at a cycle length of 1,000 msec. Functional block in the left bundle resulted in the electrocardiographic pattern of complete left bundle branch block although the block was incomplete, as demonstrated by development of functional right bundle branch block at a shorter H_1–H_2 interval. This demonstrates another type of discordance of conduction time and refractory period. Although the refractory period of the right bundle branch was shorter than that of the left, delays in the right bundle branch were greater once this refractory period was achieved.

The refractory periods of both the left and right bundles are rate-dependent: As cycle lengths shorten, refractory periods decrease.[6,7] This explains the lack of functional block at the shortest cycle length. The repetitive rhythmic ventricular aberration observed in Figure 5 can be explained by the differential effect of the cycle length upon refractory periods of the left and right bundle branches and by the effect of repetitive concealed conduction.[6,7] After long H–H intervals produced by blocked P waves during the A–V nodal Wenckebach sequences, the impulse encountered increased refractoriness in both bundle branches. The degree of delay in each bundle determined the type of aberrancy: If the delay was greater in the left bundle, a pattern of left bundle branch block re-

sulted; if the delay was greater in the right bundle, a pattern of right bundle branch block occurred. In both cases, the H–V interval was prolonged, reflecting delays in the bundle branch with less slowing. The ventricular aberration and shorter H–V interval in the third conducted beats in the Wenckebach sequence was the result of both the effect of cycle length and retrograde concealed conduction: Repetitive retrograde concealed conduction maintained the bundle branch block, and decreasing cycle length allowed the H–V interval to shorten.[6] The greater QRS duration observed in the third conducted beats (QRS complexes 3 and 10) showing right bundle branch block aberrancy can be explained by the asynchronous recovery in both bundle branches. The more frequent aberrancy of a right bundle branch block pattern after a Wenckebach block and the longer refractory period of the left bundle at the cycle lengths studied suggest that the refractory period of the right bundle was more sensitive to abrupt changes in cycle length. Greater delays in the right bundle branch system once the refractory period of this system was reached could also explain the predominance of right bundle branch aberrant conduction.

Discussion

From his analysis of electrocardiograms, Lepeschkin[1] proposed several possible combinations of incomplete block in both bundle branches. He stated that slowing of conduction in both bundle branches would produce P–R prolongation. If one bundle were delayed more than the other, the QRS configuration would reveal bundle branch block in the side showing greater delay. He also suggested that combinations of first and second degree block in both bundle branches could produce an electrocardiographic pattern of alternating bundle branch block.

Recently in a study of left bundle branch block with normal axis, Cannom et al.[8] demonstrated a leftward shift in axis with premature atrial stimulation. They suggested that in this condition, antegrade conduction was still present in the anterior fascicle and that the leftward shift in axis reflected additional conduction delays in the left anterior division. As an alternative explanation for their findings, one could postulate predivisional complete left bundle branch block. If this were the case, the impulse would have to travel from the right bundle across the ventricular septum and then spread through the peripheral Purkinje muscle network of the left ventricle. A premature impulse could encounter peripheral delays in the anterior left ventricle distal to the block with a resultant leftward shift in axis.

Our data suggest that incomplete blocks can occur in the three fascicles, thus confirming previous speculations. The measurement of refractory period by the atrial extrastimulus technique provides a means of demonstrating these incomplete blocks in patients with apparent complete bundle or fascicular block. By demonstrating that block in the opposite fascicle or bundle branch replaces the preexisting block, one can show that the blocked bundle branch or fascicle is capable of conduction.

This demonstration depends upon the presence of a discordance of conduction velocity and refractory period in the ventricular specialized conduction system: The faster conducting bundle branch or fascicle must have a longer refractory period than the incompletely blocked bundle branch or fascicle. In Patient 1 the refractory period was shorter in the incompletely blocked left bundle branch than in the right bundle branch. In Patient 2 the refractory period was shorter in the incompletely blocked anterior fascicle than in the posterior fascicle. In Patient 3, the refractory period of the left bundle branch was longer, but conduction delays were greater in the right bundle once its refractory period was achieved with an extrastimulus. Thus, a bundle or a fascicle with a longer conduction time does not necessarily have a longer refractory period. In a patient with incomplete bundle branch block, when the blocked bundle branch has a long refractory period (relative to that of the normal bundle branch), the extrastimulus technique will not demonstrate the partial block.

Bifascicular block and normal H–V interval: The demonstrated discordance of conduction velocity and refractory periods in portions of the His-Purkinje system may partially explain the recent finding of development of block distal to the His bundle in patients with bifascicular block and a normal H–V interval.[9] Although in these cases the normal H–V interval suggests a normal conduction time in the remaining functioning fascicle, it is possible that the refractory period in this fascicle is prolonged (or may become prolonged), thus predisposing to the development of complete trifascicular block. This discordance may also partially explain why complete trifascicular block may not develop in some patients with bifascicular block and a prolonged H–V interval. In these cases, although conduction velocity is depressed in the remaining functioning fascicle, the refractory period and the response of refractory period to change in cycle length of this fascicle might be normal, thus preventing development of block.

Ventricular conduction defects in arrhythmias: The existence of incomplete blocks masquerading as complete and the discordance of refractory period and conduction velocity in portions of the His-Purkinje system predispose to very complex sequences of ventricular activation, as demonstrated during Wenckebach periods in Case 3. In patients with atrial fibrillation or atrial flutter with varying block and cycle lengths that change from cycle to cycle, the potential exists for development of seemingly inexplicable changes in QRS configuration. One could easily misinterpret an electrocardiogram showing bilateral functional bundle branch block (aberrant conduction in both the left and right bundle branch systems) as a manifestation of bilateral bundle disease or multifocal premature ventricular beating. The difficulty in achieving a correct electrocardiographic diagnosis is further compounded by the

occurrence of repetitive concealed conduction maintaining a particular pattern of aberration, and by the differential responses of bundle branch refractory periods to change in cycle length. Knowledge of some of these potential difficulties should improve electrocardiographic diagnosis.

In conclusion, our study has demonstrated the following: (1) Incomplete block in a bundle branch or fascicle can produce an electrocardiographic pattern of complete fascicular or bundle branch block. (2) This incomplete block may be demonstrable with the extrastimulus technique. (3) Discordance of conduction velocity and refractory period may occur in portions of the His-Purkinje system, a bundle or fascicle with incomplete block having a shorter refractory period than a more normally conducting bundle branch or fascicle. (4) Delays in the fascicle or bundle branch with a shorter refractory period may be greater than delays in the portions of the His-Purkinje system with a longer refractory period, once the former refractory period is achieved. (5) The discordance of conduction time and refractory periods described in patients with partial bundle branch block may predispose to complex sequences of ventricular activation, particularly in supraventricular tachyarrhythmias with changing cycle length.

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Concealed Bypasses of the Atrioventricular Node in Patients with Paroxysmal Supraventricular Tachycardia Revealed by Intracardiac Electrical Stimulation and Verapamil

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Thirteen patients with paroxysmal supraventricular tachycardia were studied with use of His bundle electrograms and programmed intracardiac stimulation. No patient had evidence of either the Wolff-Parkinson-White or Lown-Ganong-Levine syndrome. During ventricular pacing at a rate of 90 to 180 beats/min retrograde conduction time increased by an average of 80 msec in eight patients; in the remaining five patients the average increase was only 9 msec. The tachycardia was terminated in all 13 patients after intravenous administration of verapamil, 10 mg. This drug acts predominantly on the atrioventricular (A–V) node, and during termination of an A–V nodal reciprocal tachycardia both the antegrade and retrograde conduction times would be expected to be prolonged. During termination of the tachycardia antegrade conduction was prolonged by an average of 43 msec and retrograde conduction by an average of 79 msec in eight patients. However, in five patients antegrade conduction was prolonged by an average of 101 msec and retrograde conduction by an average of only 3 msec. The minimal effect of this drug on retrograde conduction and the minimal increase in retrograde conduction during ventricular pacing in these five patients is strong evidence for the presence of an A–V nodal bypass that was not apparent from the surface electrocardiogram. The potential hazards should atrial fibrillation occur and allow rapid antegrade conduction in an A–V nodal bypass are discussed.

Patients with supraventricular tachycardias thought to be caused by a reciprocal mechanism can be classified in three groups: (1) Patients who manifest reciprocation that probably occurs within the atrioventricular (A–V) node.[1–5] (2) Patients with reciprocation involving the A–V node and an adjacent bypass, such as the posterior internodal tract described by James[6] and Ferrer.[7] These patients usually have a short P–R interval on the surface electrocardiogram and are thought to have the Lown-Ganong-Levine syndrome[8,9] (3) Patients who have reciprocal tachycardias involving antegrade passage of the impulse in the A–V node and retrograde conduction in a Kent bypass in the right or left A–V groove. These patients have the Wolff-Parkinson-White syndrome[10,11] and may have delta waves on the surface electrocardiogram during sinus rhythm.

In this paper we present the results of an electrophysiologic study of 13 patients with paroxysmal supraventricular tachycardia who had no evidence of an A–V nodal bypass on the surface electrocardiogram although the study elicited evidence of a bypass in 5. A reciprocal mechanism was shown to be the basis for the tachycardia in all 13 patients.

From the Departments of Cardiology, Guy's Hospital and the London Hospital, London, England. This project was supported by a British Heart Foundation Grant and by a grant from Knoll A. G., Ludwigshafen, West Germany. Manuscript accepted September 25, 1973.

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TABLE I

Clinical and Electrocardiographic Data in 13 Cases

Case no.	Age (yr) & Sex	Cause of Tachycardia	P–R Interval* (sec)
1	62M	Coronary artery disease	0.16
2	57F	Unknown	0.14
3	45M	Coronary artery disease	0.18
4	22F	Unknown	0.14
5	35M	Unknown	0.15
6	60M	Unknown	0.18
7	45F	Coronary artery disease	0.13
8	44M	Unknown	0.20
9	65F	Unknown	0.19
10	57M	Unknown	0.16
11	46F	Unknown	0.14
12	53M	Unknown	0.17
13	49F	Unknown	0.15

* P–R intervals were all within normal limits (0.12 second considered lower limit of normal). No delta waves indicating ventricular preexcitation were seen.

Material and Methods

Thirteen patients, 7 male and 6 female, were studied. The relevant clinical and electrocardiographic data are presented in Table I. All 13 patients had documented attacks of paroxysmal supraventricular tachycardia. In 3 patients coronary artery disease was thought to be the underlying cause; in the remaining 10 patients no specific etiology was discovered.

Informed consent was obtained in all cases, and an electrophysiologic study was carried out with patients in the postabsorptive, nonsedated state. Three electrode catheters were introduced percutaneously through one or both femoral veins. Two catheters were positioned in the right atrium, one hexapolar catheter for recording the high and low atrial electrograms and the other for pacing the atrium. The third catheter, positioned across the tricuspid valve, was used to record the His bundle electrogram by the technique of Scherlag et al.[12] The recordings were made on an eight channel Elema Mingograf 81. A surface electrocardiogram was recorded simultaneously with a high and low atrial electrogram and the His bundle electrogram. The His bundle electrogram was recorded with the frequency response set at 45 to 500 cycles/sec.

A Devices 4270 stimulator (Devices Instruments Limited, Welwyn Garden City, Herts, England) was used for atrial and ventricular pacing. The heart was driven at a constant rate, thus preventing changes in excitability or refractoriness due to irregularities in rhythm. Single or double atrial or ventricular premature beats were delivered after every eighth beat of the basic driving rhythm. A variable delay circuit triggered by either the R wave of the surface electrocardiogram or the right atrial electrogram was used so that the premature beats could be delivered in the cardiac cycle at a preset delay after the preceding driving beat. In each patient the mode of initiation and termination of the tachycardia and the effect of atrial and ventricular premature beats on the basic rhythm during tachycardia were studied. Atrial and ventricular pacing at a rate of 90 to 180 beats/min was performed to determine the characteristics of antegrade and retrograde conduction. Finally, after initiation of the tachycardia by an appropriate premature beat, the mode of termination after an intravenous injection of 10 mg of verapamil (Cordilox®, Knoll AG, West Germany) was studied. This drug was originally introduced as an antianginal agent[13] but has recently been found to be an effective antiarrhythmic agent in man.[14] Verapamil is not a beta receptor blocking drug and its mode of action does not appear to be similar to that of quinidine.[15] It has been shown to interfere with the transport of calcium across the cell membrane, with the implication that calcium currents may contribute to abnormalities of cardiac rhythm.[15]

Results

Electrocardiograms

The relevant details are presented in Table I. No patient had evidence of either the Lown-Ganong-Levine syndrome (manifested by a P–R interval of less than 0.12 second) or the Wolff-Parkinson-White syndrome (manifested by a short P–R interval and a delta wave).

Electrophysiologic Study

Initiation of tachycardia: In all 13 patients the tachycardia could be initiated by suitably timed single or double atrial or ventricular premature beats.

During tachycardia: Atrial and ventricular premature beats that were induced during tachycardia

TABLE II

Antegrade Conduction Time During Atrial Pacing in 13 Cases

Case no.	Pacing Rate	P or St–H Interval* (msec)
1	100	155
	160	190
2	90	90
	180	165
3	90	100
	120	145
4	110	130
	160	190
5	100	120
	175	194
6	Not performed	
7	80	110
	120	140
8	Not performed	
9	100	205
	175	274
10	100	132
	140	172
11	100	175
	120	190
12	100	100
	140	240
13	Not performed	

* The average increase in antegrade conduction time was 53 msec in Cases 1 through 5 and Case 7 and 66 msec in Cases 9 through 12. P or St–H = time in milliseconds from the onset of the P wave on the surface electrocardiogram or the atrial pacing stimulus artefact to the His deflection on the His bundle electrogram.

TABLE III

Retrograde Conduction Time During Ventricular Pacing in 13 Cases

Case no.	Pacing Rate	V–A Interval* (msec)
	A. Cases 1 to 8	
1	90	140
	180	220
2	100	130
	160	185
3	100	205
	180	290
4	90	100
	180	180
5	100	165
	180	235
6	90	125
	175	210
7	100	75
	180	165
8	120	130
	180	225
	B. Cases 9 to 13	
9	120	150
	170	158
10	90	130
	180	138
11	100	135
	180	150
12	90	125
	170	135
13	100	128
	165	132

*The average increase in retrograde conduction time (V–A interval) was 80 msec in Cases 1 to 8 and 9 msec in Cases 9 to 13. V–A interval = time in milliseconds from the onset of ventricular activation to the intrinsic deflection in the low atrial electrogram.

TABLE IV

Antegrade and Retrograde Conduction Times in 13 Cases Before Administration of Verapamil and One Cycle Before Termination of Tachycardia by Verapamil

	Before Verapamil		One Cycle Before Termination of Tachycardia by Verapamil	
Case no.	A′–H (msec)	H–A′ (msec)	A′–H (msec)	H–A′ (msec)
	A. Cases 1 to 8			
1	285	60	350	110
2	50	372	70	420
3	172	180	224	245
4	65	232	85	310
5	160	170	205	265
6	225	110	272	215
7	290	50	340	150
8	205	100	250	191
Average increase in antegrade conduction (A′–H) = 43 msec.				
Average increase in retrograde conduction (H–A′) = 79 msec.				
	B. Cases 9 to 13			
9	165	100	233	110
10	390	60	442	60
11	320	40	415	40
12	275	45	450	45
13	255	65	370	70
Average increase in antegrade conduction (A′–H) = 101 msec.				
Average increase in retrograde conduction (H–A′) = 3 msec.				

but did not terminate the tachycardia were followed by pauses that were less than compensatory.

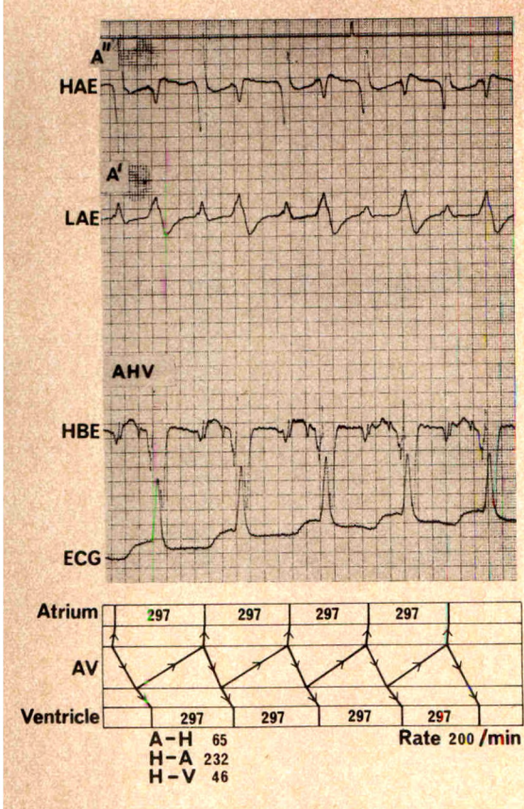
Termination of the tachycardia: In all 13 patients the tachycardia could be terminated by suitably timed single or double atrial or ventricular premature beats.

Atrial pacing: Atrial pacing at a rate of 90 to 180 beats/min was carried out in all patients except Patients 6, 8 and 13 (Table II). In Patients 1 to 5 and 7 the average increase in antegrade conduction time was 53 msec and in Patients 9 to 12 the average increase was 66 msec. These results are in accord with increasing delay in the atrioventricular (A–V) node due to increasing driving rates during atrial pacing[16]; they suggest that in these 10 patients the antegrade passage of the impulse occurred through the A–V node.

Ventricular pacing: All 13 patients underwent ventricular pacing. Retrograde conduction time in all patients except Patients 2 and 4 was longer during ventricular pacing at 180 beats/min than during tachycardia (Tables III and IV). This difference occurred because during tachycardia retrograde conduction is assessed by measuring the time from His bundle depolarization to low atrial depolarization (H–A interval) whereas during ventricular pacing it is measured from the stimulus artefact at the onset of ventricular activation to the low atrial depolarization (V–A interval); thus, an additional conduction time during ventricular activation and conduction through the bundle branches to the His bundle is incorporated in this measurement.

Table IIIA lists the values for retrograde conduction time in Patients 1 to 8. Right ventricular pacing was performed at a rate of 90 to 180 beats/min, and retrograde conduction time was measured from the onset of ventricular activation to the intrinsic deflection in the low atrial electrogram. In these patients the average increase in retrograde conduction time was 80 msec; this increase was attributed to greater delay within the A–V node as a result of the increased ventricular rate.

In patients with a normal conduction system retrograde conduction time has been shown to increase when ventricular premature beats are induced progressively earlier in the cardiac cycle during ventricular pacing.[1] This finding accords with normal values obtained in our laboratory for the increase in retrograde conduction time observed when ventricular premature beats[17] are induced progressively earlier



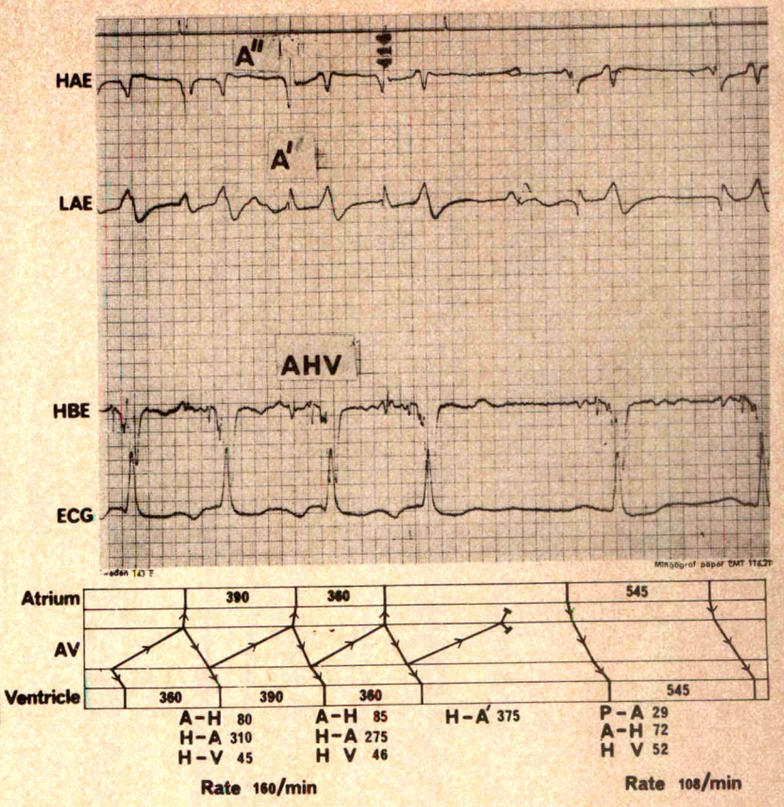


FIGURE 1 (left). Case 4. Tracings obtained during tachycardia before verapamil was administered. A = retrograde atrial depolarization on the His bundle electrogram (HBE). A′ = retrograde atrial depolarization in the low right atrium (LAE). A″ = retrograde atrial depolarization in the high right atrium (HAE), A–H = antegrade conduction in milliseconds from the low atrial depolarization as recorded on the His bundle electrogram to the His bundle deflection; AV = atrioventricular; ECG = surface electrocardiogram; H = His bundle deflection; H–A = retrograde conduction in milliseconds from the His bundle deflection to the low atrial depolarization.

FIGURE 2 (right). Case 4. Tracings obtained during termination of the tachycardia with verapamil. The tachycardia is terminated after the fourth beat with block in the retrograde pathway. The fifth and sixth beats are sinus in origin.

and when the ventricular rate is increased during ventricular pacing.

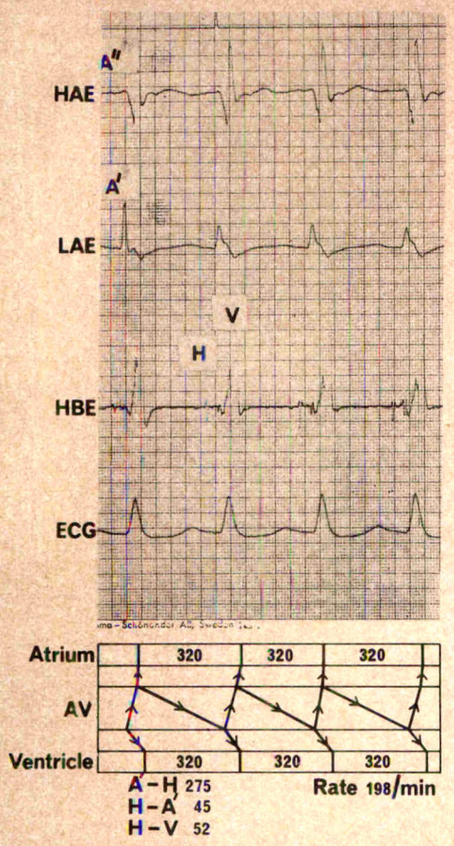
Table IIIB lists the comparable values for retrograde conduction time in Patients 9 to 13. The average increase in these patients was only 9 msec. This finding suggests that the impulse was returning to the atrium by a pathway that did not have the properties of the A–V node; hence, retrograde conduction time was not prolonged as ventricular rates increased.

Termination of the tachycardia with verapamil: After initiation of the tachycardia by a suitably timed atrial or ventricular premature beat, 10 mg of verapamil was administered intravenously to all 13 patients. In each patient the tachycardia was terminated 60 to 90 seconds later. Figure 1 shows the intracardiac recording obtained from Patient 4 during tachycardia, and Figure 2 shows recordings obtained from the same patient during termination of the tachycardia after administration of verapamil. The antegrade conduction time (A–H interval) was prolonged from 65 to 85 msec and retrograde conduction time (H–A interval) from 232 to 310 msec. The tachycardia was terminated with block in the retrograde pathway as illustrated on the ladder diagram.

Table IVA lists the effects of verapamil on antegrade and retrograde conduction during termination of the tachycardias in Patients 1 to 8. Antegrade conduction is prolonged by an average of 43 msec and retrograde conduction by an average of 79 msec. His bundle studies[17,18] have shown that verapamil acts predominantly by prolonging antegrade conduction within the A–V node in patients with a normal conduction system. In such patients it also prolongs retrograde conduction during ventricular pacing and after ventricular premature beats. This prolongation in retrograde conduction is thought to occur within the A–V node.[17] Therefore our findings in Patients 1 to 8 suggest that both the antegrade and retrograde pathways of the reciprocal circuit in tachycardia lie within the A–V node.

Figure 3 shows the intracardiac recordings obtained from Patient 12 during tachycardia, and Figure 4 shows the recordings obtained from the same patient during termination of the tachycardia after administration of verapamil. Antegrade conduction (A′–H interval) was prolonged from 275 to 450 msec whereas retrograde conduction (H–A′) was unchanged at 45 msec before and after administration of verapamil.

Table IVB lists the effects of verapamil on antegrade and retrograde conduction times in Patients 9



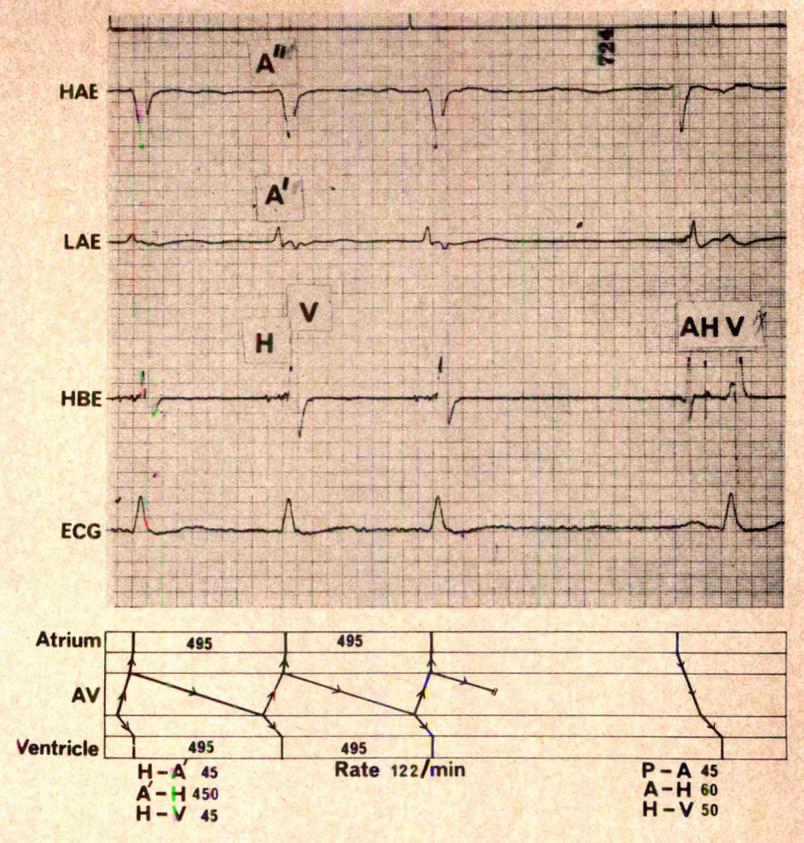


FIGURE 3 (left). Case 12. Tracings obtained during tachycardia before administration of verapamil. A′–H = antegrade conduction in milliseconds from the low atrial depolarization on the low atrial electrogram to the His deflection; H–A′ = retrograde conduction in milliseconds as measured from the His deflection to the low atrial depolarization on the low atrial electrogram.

FIGURE 4 (right). Case 12. Tracings obtained during termination of the tachycardia after administration of verapamil. The tachycardia is terminated after the third beat with block in the antegrade pathway. The fourth beat is sinus in origin.

to 13. Antegrade conduction was prolonged by an average of 101 msec whereas retrograde conduction was prolonged by an average of only 3 msec. This small effect on the retrograde conduction time after the administration of a drug known to prolong A–V nodal conduction time suggests that the retrograde impulse was not passing to the atria by way of the A–V node but was bypassing it in a pathway unaffected by verapamil.

Discussion

Evidence for reciprocating tachycardia: To diagnose a reciprocal mechanism as the underlying basis of a supraventricular tachycardia, three criteria should be fulfilled: (1) It should be possible to initiate the tachycardia with a suitably timed single or double atrial or ventricular premature beat; (2) during tachycardia, induced atrial or ventricular premature beats that do not terminate the tachycardia should be followed by pauses that are less than compensatory; and (3) it should be possible to terminate the tachycardia with single or double atrial or ventricular premature beats.[19] These criteria were met in all 13 cases.

In the absence of evidence of preexcitation on the surface electrocardiogram (a short P–R interval or short P–R interval and delta wave, for example) patients with reciprocating paroxysmal supraventricular tachycardia are thought to have the antegrade and retrograde pathways of the reciprocal circuit within the A–V node.[1–5] None of our 13 patients studied had evidence of preexcitation on the surface electrocardiogram. However, as a result of the electrophysiologic study Patients 1 to 8 appeared to have both pathways of the reciprocal circuit within the A–V node and Patients 9 to 13 had evidence of an A–V nodal bypass such that during reciprocating tachycardia the antegrade pathway was within the

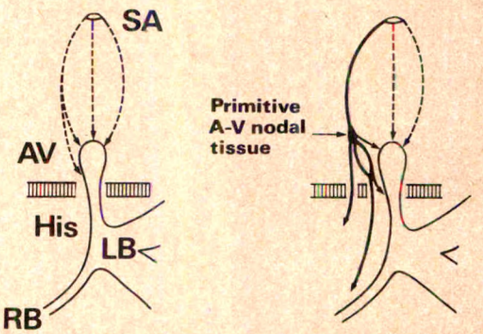


FIGURE 5. Diagram showing the specialized conduction pathways in the normal heart **(left)** and the abnormal pathways arising from primitive A–V nodal tissue and bypassing the true A–V node to enter the septum and bundle of His **(right).** See text.

A–V node and the retrograde pathway in an extranodal bypass. In the absence of evidence for the Wolff-Parkinson-White syndrome this bypass was thought to be closely adjacent to the A–V node.

The significance of a bypass that does not have the properties of A–V nodal tissue is that it provides an alternative conduction pathway down which impulses can pass and activate the ventricles. Likewise an impulse can pass in retrograde manner from the ventricles in the bypass and activate the atria. In Patients 9 to 13 antegrade conduction appeared to occur by way of the A–V node-His pathway alone both during atrial pacing and tachycardia, whereas only retrograde conduction occurred in the bypass. It is not known why retrograde but not antegrade conduction occurs in the bypass, but this phenomenon may be due to "mismatched impedance."[20]

Clinical implications: Under normal circumstances the ventricles are protected by the A–V node from bombardment by impulses traveling at high frequency, as occurs in atrial fibrillation. However, if an A–V nodal bypass is present, particularly if it has a short refractory period, then under circumstances in which the mismatched impedance might be dissipated, impulses may pass to the ventricles at high frequency by way of this bypass and the risk of ventricular fibrillation is then present. This situation has been described in the Wolff-Parkinson-White syndrome.[21,22] We believe that patients with A–V nodal bypasses of the type described here are at risk should atrial fibrillation suddenly develop. There is also an increased risk that atrial fibrillation will develop in this group of patients: An early ventricular extrasystole can be conducted rapidly to the atria, in the bypass, arrive in the atrial vulnerable period and precipitate atrial fibrillation[23] which, in turn, may lead to ventricular fibrillation for the reasons given.

Figure 5 illustrates the anatomy of the conduction system in a 35 year old man who had atrial fibrillation of unknown etiology and complained of several syncopal episodes on exertion; during one of these he died. Histologic examination of his heart demonstrated the presence of primitive A–V nodal tissue leading to tracts that bypassed the A–V node and joined the main bundle of His and ventricular septum. We postulate that this man's death was due to ventricular fibrillation after rapid antegrade conduction of impulses from the fibrillating atria down the bypass tracts to the ventricles. Our electrophysiologic study provided evidence for the occurrence of retrograde but not antegrade conduction by way of a bypass tract. We are unable to determine the physiologic conditions required for the occurrence of antegrade conduction in the bypass in the presence of atrial fibrillation with its potential for inducing ventricular fibrillation. It may be that increased sympathetic activity plays an important part in this respect since the syncopal episodes and death of the patient described occurred during exercise.

Acknowledgment

We are grateful to Dr. M. J. Davies, St. Georges Hospital, London S.W.1, England, for the histologic studies reported here.

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Electrophysiologic Properties of Procainamide in Man

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The electrophysiologic properties of procainamide were studied in 16 patients and correlated with plasma levels. Procainamide caused a minimal prolongation of atrioventricular (A–V) nodal conduction in 11 of 16 patients during sinus rhythm, but His-Purkinje conduction time was significantly prolonged in 15 of 16 patients. The effective refractory period of the atrium was prolonged by procainamide in 14 of 16 patients. The effective refractory period of the A–V node decreased in 8 of 9 patients. This may have been due to (1) anticholinergic properties of procainamide, (2) production of an A–V nodal "gap" by procainamide, or (3) an apparent A–V nodal block that actually represented decremental conduction in the His bundle; procainamide then caused delay in the A–V node allowing improved intra-His conduction and ventricular depolarization. The relative refractory period of the His-Purkinje system was prolonged in 10 of 11 patients. The effective refractory period was prolonged in one patient, unchanged in a second and apparently shortened in a third. In this third patient, procainamide produced a marked delay in proximal His-Purkinje conduction allowing a distal area of refractoriness to recover, thus causing apparent shortening of the effective refractory period. Plasma levels averaged 7.1 mg/liter at the end of the study; no toxicity was noted.

Procainamide is one of the oldest and most useful antiarrhythmic agents.[1–8] Although its clinical efficacy has been well established, its effects on the electrophysiologic properties of various portions of the atrioventricular (A–V) conducting system in man have not been extensively evaluated.[9,10] Most of our knowledge is based on studies of intact animals and tissue preparations.[11-16] These and more recent studies[17–22] have attributed the following effects to procainamide: (1) decreased automaticity, (2) impaired A–V conduction, (3) increased refractoriness, and (4) decreased membrane responsiveness. Several recent articles[23–29] have examined the mechanisms of arrhythmias and the manner in which the electrophysiologic properties of procainamide might influence various arrhythmias. Because of the persistent question of relevance of animal and in vitro studies to effects in man, in this study we evaluated some of the electrophysiologic properties of procainamide in man and correlated them with plasma levels of the drug.

Materials and Methods

Sixteen patients underwent right heart catheterization in the nonsedated postabsorptive state after informed consent was obtained. The clinical data of these patients are given in Table I. No patient was receiving antiarrhythmic agents or digitalis at the time of the study; two patients had discontinued digoxin 3 days before catheterization.

A quadripolar electrode catheter was inserted percutaneously into an antecubital vein and positioned fluoroscopically against the lateral wall of the right atrium. The distal two electrodes were used to pace the atrium and the

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TABLE I

Clinical Data

Case no.	Age (yr)	Type of Heart Disease	Reason for Catheterization
1	60	ASHD	Angina pacing, LAH
2	56	ASHD	VPCs
3	50	? ASHD	Angina pacing, LAH
4	63	AS, ? ASHD	Angina pacing, LAH
5	43	? ASHD	Angina pacing
6	46	ASHD	Angina pacing
7	59	ASHD	Angina pacing
8	54	? ASHD	Angina pacing
9	38	HCVD	Angina pacing, VPCs
10	39	COPD	Angina pacing
11	73	None	Palpitations, ? PAT
12	49	None	VPCs
13	39	? ASHD	VPCs, APCs, JPCs, angina pacing
14	44	ASHD	Angina pacing
15	59	? ASHD	Angina pacing
16	43	? ASHD	Multifocal VPCs, angina pacing

AS = aortic stenosis; ASHD = atherosclerotic heart disease; COPD = chronic obstructive pulmonary disease; HCVD = hypertensive cardiovascular disease; JPCs = junctional premature contractions; LAH = left anterior hemiblock; PAT = paroxysmal atrial tachycardia; VPCs = ventricular premature contractions.

proximal pair was used to record a high right atrial electrogram. His bundle electrograms were obtained using a tripolar electrode catheter, as previously described.[30] Four surface electrocardiographic leads were simultaneously recorded (leads I, II, III and V_1). Time lines were generated at 10 and 100 msec.

Conduction studies were carried out during sinus rhythm and at various paced atrial rates up to a maximum of 180 beats/min. Atrial stimulation was performed using a programmed digital stimulator that delivered impulses of 1.5 msec duration at approximately twice diastolic threshold. Measurements of A–V nodal and His-Purkinje conduction times were made at each paced cycle length. The A–H interval as measured in the His bundle electrogram represented conduction time through the A–V node (normal 60 to 140 msec); the H–V interval measured conduction through the His-Purkinje system (normal 35 to 55 msec).

With use of the atrial extrastimulus method,[31] the refractory periods of the atrium, A–V node and His-Purkinje system were determined at various paced cycle lengths to avoid the effect of changing cycle length on refractoriness. Progressively premature atrial depolarizations (A_2) were introduced after every eighth paced atrial beat (A_1) until the effective refractory period of the atrium was reached.

After the initial studies were completed, a control blood sample was withdrawn in heparinized tubes. Each patient received 500 mg of procainamide intravenously at a rate of approximately 50 mg/min. Blood pressure and heart rate were monitored.

Shortly after the end of the infusion another blood sample was drawn. Refractory periods and conduction studies were then repeated with additional blood samples drawn at approximately 10 to 15 minute intervals until the studies were completed, usually within 30 minutes. Plasma levels were analyzed spectrophotometrically according to methods outlined by Koch-Weser.[32] All data were stored on magnetic tape (North American Phillips Tape Recorder, Shelton, Conn.) and later retrieved at paper speeds of 150 and 200 mm/sec (Electronics for Medicine).

Definition of Terms

The effective refractory period of the atrium is defined as the longest S_1–S_2 interval at which S_2 fails to depolarize the atrium, S representing the stimulus artifact.

The effective refractory period of the A–V node is defined as the longest A_1–A_2 interval at which A_2 fails to propagate to the His-Purkinje system.

The functional refractory period of the A–V node is defined as the shortest H_1–H_2 interval that results from any A_1–A_2 interval.

The effective refractory period of the His-Purkinje system is defined as the longest H_1–H_2 interval at which H_2 fails to conduct to the ventricles.

The relative refractory period of the His-Purkinje system is defined as the longest H_1–H_2 interval at which H_2 conducts to the ventricles with a longer H–V time than that of the basic drive beat or with a QRS complex of aberrant configuration.*

Results

Spontaneous sinus rate: Procainamide produced no change or a slight increase in spontaneous heart rate. The mean change was a 7 percent increase in heart rate from the control level. Only two patients (Cases 11 and 16) had increases of 15 percent or more.

Conduction

Conduction times: Conduction times through the A–V node and His-Purkinje system were normal in all but one patient (Case 2, H–V interval 70 msec) before administration of procainamide.

A–V nodal conduction: After administration of procainamide 11 of 16 patients showed prolongation of the A–H interval during sinus rhythm; in 4 there was no change, and in 1 patient a decrease. The mean increase was 7 msec (7 percent) (range of 5 to 25 msec). In the 11 patients whose A–V nodal conduction time was studied during atrial pacing, procainamide produced more variable results; the A–H interval increased in 5, decreased in 4, and did not change in 2 when compared to control values at the same paced rates. Thus, some patients in whom procainamide prolonged the A–H interval during sinus rhythm showed no change or a decrease in the A–H interval at paced atrial rates comparable to control rates.

His-Purkinje conduction: During sinus rhythm procainamide caused H–V prolongation (10 to 33 percent) in 15 of 16 patients. In the remaining patient no change was noted. Pacing produced no further changes. There was a mean increase of 9 msec (19

* Although the His-Purkinje system is a trifascicular system, in the absence of multiple recording sites along individual fascicles it is impossible to measure the effective refractory period versus the relative refractory period of any given fascicle. Thus, for the purpose of this study we elected to consider the His-Purkinje system a single functioning unit.

TABLE II

Effects of Procainamide on Refractoriness

Case no.	Paced Cycle Length	ERP of Atrium		ERP of AVN		FRP of AVN		ERP of HPS		RRP	HPS
		B	A	B	A	B	A	B	A	B	A
1	700	260	310	...	...	380	370	...	...	420	440
	600	250	300	...	...	335	375	...	...	410	420
2	600	270	290	...	...	410	400	...	...	...	...
	550	260	270	...	...	415	410	...	...	...	...
	500	260	270	...	...	400	400	...	...	...	...
3	700	220	240	310	315	440	410	...	...	440	450
	600	230	240	330	320	445	430	...	...	...	...
	500	210	260	340	335	440	430	...	...	...	...
4	800	280	280	...	...	445	450	...	...	500	515
	600	240	260	...	...	425	430	...	...	450	475
5	750	280	290	...	...	400	395	400	400	415	420
	700	270	270	...	...	390	390	...	...	390	410
	600	270	270	320	<315	390	390	...	...	...	...
6	700	255	290	...	...	355	365	360	390	380	455
	650	250	280	...	...	355	370	<355	370	365	390
	600	240	280	...	...	360	380	...	...	<360	388
7	900	<250	280	320	310	460	480	515	480	520	560
	800	<250	250	330	<250	470	460	490	<460	500	530
	700	280	240	340	<230	460	460	...	...	475	485
8	800	270	290	...	...	425	450	...	...	460	480
	700	270	285	...	...	415	445	...	...	425	450
	600	260	270	...	...	400	420	...	...	...	...
9	600	230	260	365	<285	450	340	...	...	450	390
10	600	280	300	...	...	320	410	...	...	425	425
11	600	225	280	290	<280	370	375	...	...	...	...
12	600	235	215	270	<215	340	340	...	...	355	390
13	900	380	400	...	...	455	462	...	...	472	490
	800	330	360	...	...	430	430	...	...	450	460
	700	330	360	...	...	415	412	...	...	415	425
	500	280	300	...	...	365	400	...	...	415	425
14	900	270	330	545	390	590	500	...	...	...	...
	800	300	320	550	390	600	510	...	...	...	...
15	800	290	310	400	<290	560	495	...	...	560	500
	700	290	300	420	370	580	530	...	...	...	...
	600	270	280	460	360	575	530	...	...	...	...
16	800	2000	220	280	260	450	470	...	...	490	495
	600	190	190	300	280	415	435	...	...	...	...
	500	190	200	290	270	410	420	...	...	...	...

All measurements are expressed in milliseconds.

A = after procainamide; AVN = A–V node; B = before procainamide; ERP = effective refractory period; FRP = functional refractory period; HPS = His-Purkinje system; RRP = relative refractory period.

percent) in the H–V interval as a group, and in five patients (Cases 3, 7, 9, 13 and 15) procainamide produced abnormal His-Purkinje conduction times (greater than 55 msec). In the single patient (Case 2) with a prolonged control H–V interval, procainamide further increased this interval by 15 msec. Procainamide caused no change in QRS configuration in any patient and had a minimal effect on QRS duration, causing an increase of 20 msec or more in only three patients (Cases 6, 9 and 15), none of whom had a QRS duration exceeding 0.12 second.

Refractory Periods

Table II lists the effects of procainamide on refractoriness in all patients at various paced cycle lengths.

Effective refractory period of the atrium: Procainamide increased the effective refractory period of the atrium in 14 of 16 patients. The effective refractory period decreased in only one patient and was unchanged in the remaining patient. The mean change was +31 msec.

Effective refractory period of the A–V node: The effective refractory period of the A–V node could be measured in only nine patients. In the remaining patients the effective refractory period of the atrium was reached before that of the A–V node. The effective refractory period of the A–V node was decreased in eight of nine patients and was variably altered in one, depending on the paced cycle length. The mean decrease in the effective refractory period was 55

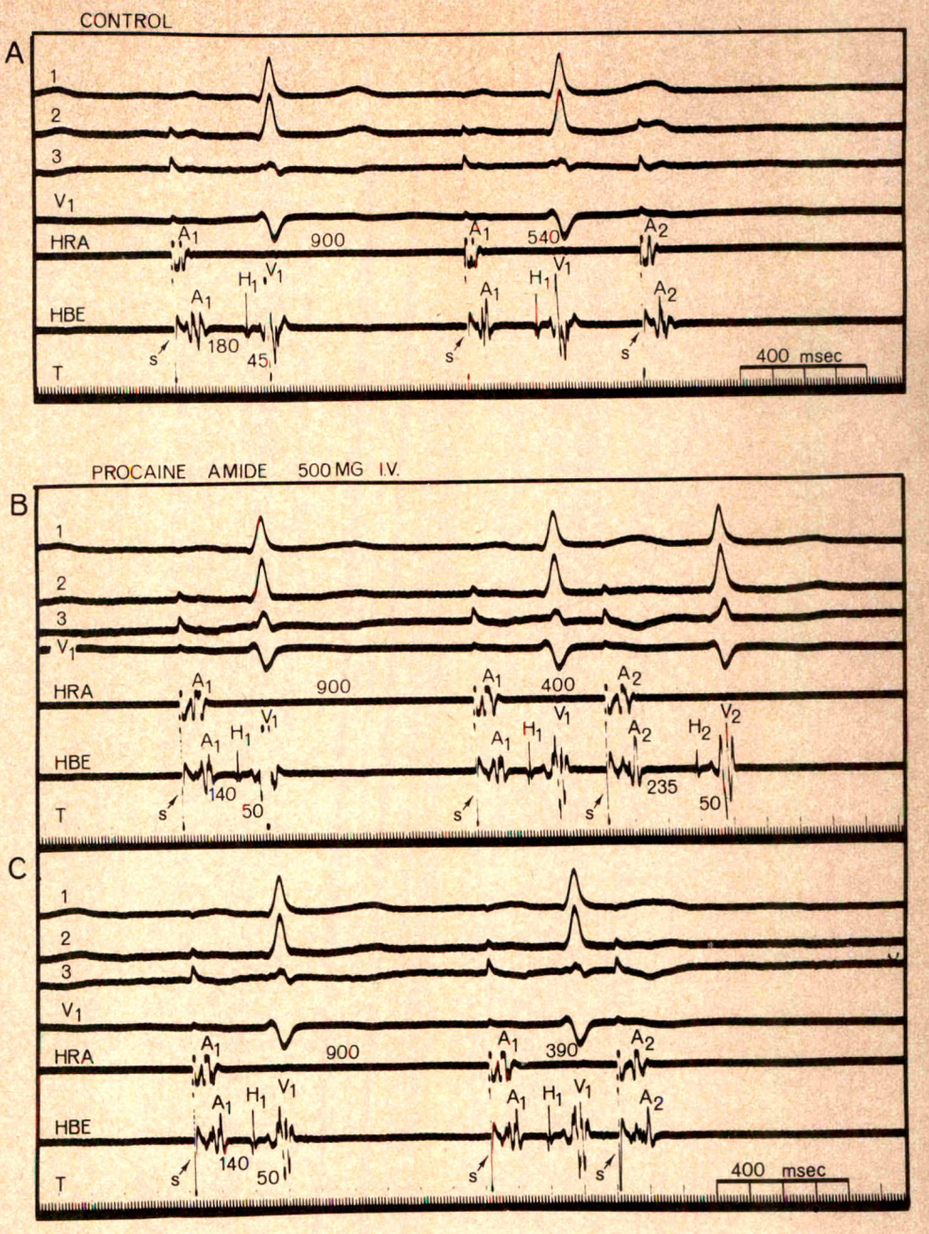

FIGURE 1. Effects of procainamide on the effective refractory period of the A–V node. Each panel is organized as follows: from top to bottom, standard leads I, II, III, V_1, high right atrial electrogram (HRA), His bundle electrogram (HBE) and time lines (T) of 10 and 100 msec. The basic paced atrial cycle length is 900 msec. In the control panel **(A)** the effective refractory period of the A–V node is reached at an atrial coupling interval (A_1–A_2) of 540 msec. After administration of procainamide, A_2 continues to conduct to the His-Purkinje system at an A_1–A_2 interval of 400 msec **(B).** When the A_1–A_2 interval is decreased to 390 msec **(C)** block of A_2 above the His bundle occurs and the effective refractory period of the A–V node is reached. Thus, procainamide shortened the effective refractory period of the A–V node by 150 msec. The 40 msec decrease in the A–H interval of the basic drive beat produced by procainamide is compatible with the anticholinergic properties of the drug (see Discussion). The H_1–V_1 interval was prolonged by 5 msec after infusion of procainamide. s = stimulus.

msec. Two patients (Cases 14 and 15) had a decrease of greater than 100 msec at the slowest paced cycle length, and in both patients A–V nodal conduction was enhanced during atrial pacing compared to control values. The results from one of these patients are shown in Figure 1.

Functional refractory period of the A–V node: Procainamide had no consistent effects on the functional refractory period of the A–V node although there was a mean increase of 10 msec. There was also no consistent relation between the effects of procainamide on the effective and functional refractory periods of the A–V node.

Relative refractory period of the His-Purkinje system: The relative refractory period increased in 10 of 11 patients by a mean of 18 msec. In one patient there was no change. In an additional two patients the effect of procainamide on the relative refractory period could not be analyzed because a comparable H_1–H_2 interval was not reached in the control study. Figure 2 is representative and demonstrates that procainamide prolonged the relative refractory period by 40 msec.

Effective refractory period of the His-Purkinje system: Only three patients had block within the His-Purkinje system during control conditions. In one patient at a paced atrial rate just above sinus rate the effective refractory period of the His-Purkinje system was increased by 30 msec (Fig. 3); at a slightly shorter paced cycle length, at which no block within the His-Purkinje system was noted during the control period, procainamide induced block within the His-Purkinje system. In the second patient the effective refractory period of the His-Purkinje sys-

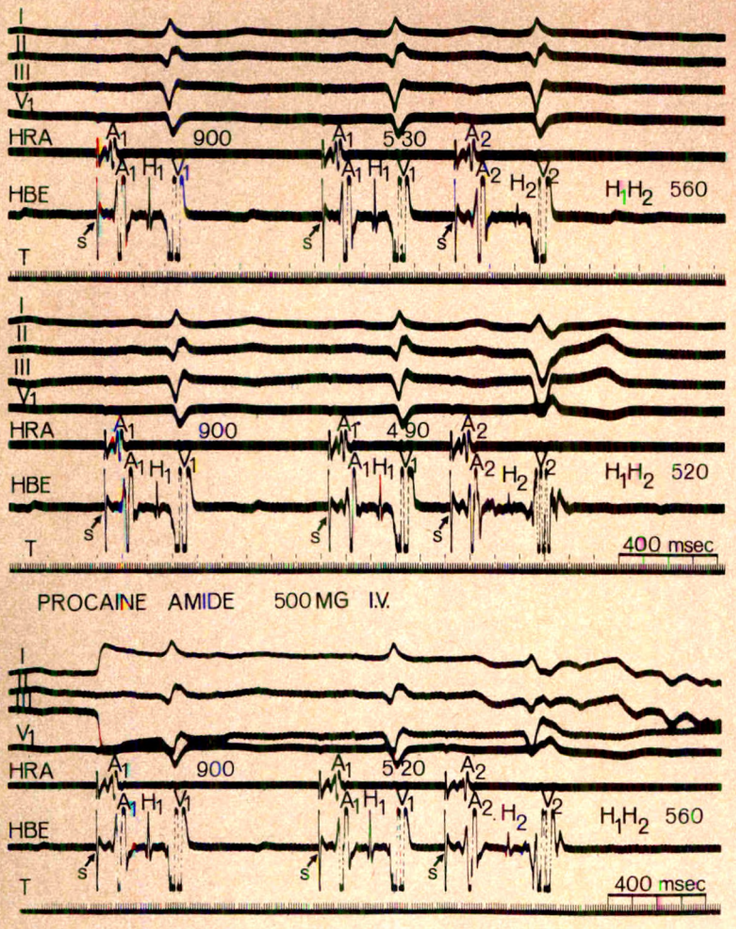

FIGURE 2. Effect of procainamide on the relative refractory period of the His-Purkinje system. The basic paced atrial cycle length is 900 msec. In control panel **(top),** A_2 is introduced at an atrial coupling interval (A_1–A_2) of 530 msec. The H_1–H_2 interval is 560 msec and the QRS configuration is the same as that of the basic drive beat. As the A_1–A_2 interval is decreased to 490 msec **(center panel)** the resulting QRS complex is aberrant with a configuration of right bundle branch block and left axis deviation. The critical H_1–H_2 interval is 520 msec and defines the relative refractory period of the His-Purkinje system during the control period. After infusion of procainamide **(bottom panel)** at an H_1–H_2 interval of 560 msec the QRS complex manifests a configuration of right bundle branch block and left axis deviation; at this H_1–H_2 interval during the control period the QRS configuration was normal. Therefore, procainamide produced a 40 msec increase in the relative refractory period of the His-Purkinje system.

tem was unchanged. In the third patient procainamide appeared to decrease the effective refractory period by 35 msec at a basic paced cycle length just above sinus rate; at a faster paced cycle length procainamide prevented block within the His-Purkinje system at any coupling interval (Fig. 4). However, in this latter case procainamide induced a marked prolongation between the His and right bundle potentials.

Effect of changing cycle lengths on refractoriness: In 12 patients refractory period studies were carried out at two or more cycle lengths. In 11 of 12 patients the effective refractory period of the atrium decreased at faster rates. In the remaining patient atrial fibrillation occurred, preventing accurate analysis. The effective refractory period of the A–V node increased in 6 of 6 patients as atrial cycle length decreased. Paced atrial cycle lengths had variable effects on the functional refractory period of the A–V node; shorter cycle lengths decreased this period in seven, increased it in three, and did not change it in two. Both the effective and relative refractory periods of the His-Purkinje system decreased as the paced atrial cycle length was decreased. Procainamide did not significantly alter these relations.

Plasma levels of procainamide: Table III lists the plasma levels of procainamide in our patients after infusion and at the end of the study.

Side effects: No patient experienced procainamide toxicity. Although in most patients the blood pressure decreased approximately 10 mm Hg during infusion of procainamide, no patient had significant hypotension. No patient manifested widening of the QRS interval of 25 percent or more or demonstrated ventricular irritability. There were no central nervous system or gastrointestinal complaints.

Discussion

Our results on the effects of procainamide on conduction through the A–V node and His-Purkinje system are similar to those reported by Rosen et al.,[9] who made similar measurements in man. In both studies procainamide produced a variable prolongation of A–V nodal conduction time. Other studies[1,5,12,15,18,19,21,24,27,29] have demonstrated a more consistent prolongation of A–V nodal conduction time in animals, but the doses of procainamide used were higher than those used in man. Prolongation of His-Purkinje system conduction time has been a consistent finding in man as well as in animals and in vitro tissue preparations.[1,2,4,7,15,16,18,19,21,23,24,27] In our study, procainamide did not produce significant changes in QRS duration and configuration, thus suggesting that the drug caused a uniform delay in

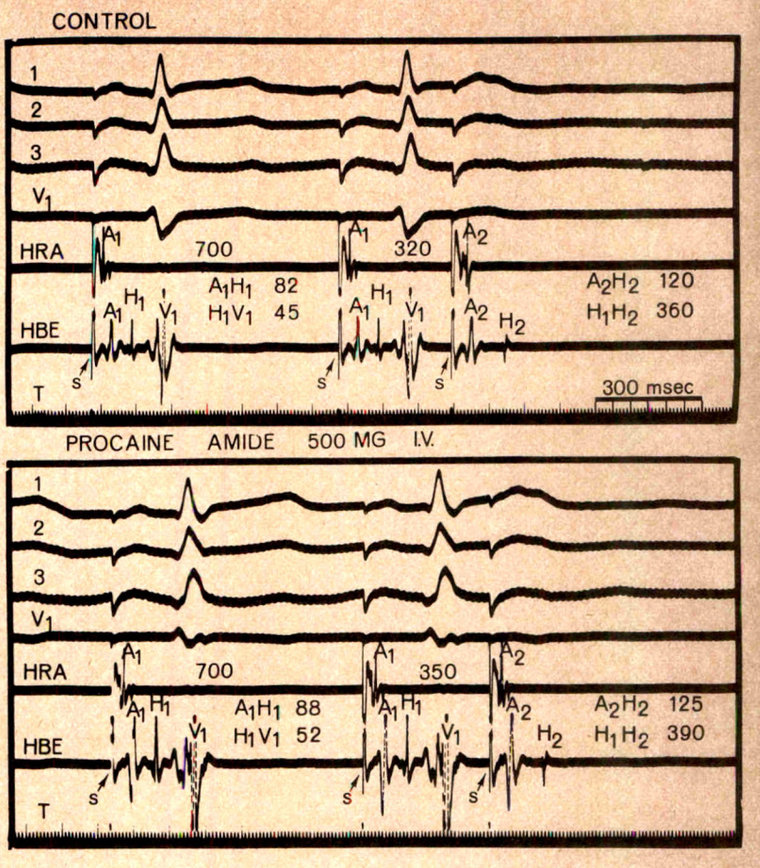

FIGURE 3. Effect of procainamide on the effective refractory period of the His-Purkinje system. The basic paced atrial cycle length is 700 msec. During control studies block developed within the His-Purkinje system at an A_1–A_2 interval of 320 msec. The H_1–H_2 interval is 360 msec and defines the effective refractory period of the His-Purkinje system. After infusion of procainamide, at a less premature atrial coupling interval (A_1–A_2 interval 350 msec), block within the His-Purkinje system is noted; the H_1–H_2 interval is 390 msec. Thus, procainamide increased the effective refractory period of the His-Purkinje system by 30 msec. Conduction time through the A–V node and His-Purkinje system during the basic drive beats (A_1–H_1 and H_1–V_1 respectively) was prolonged by procainamide.

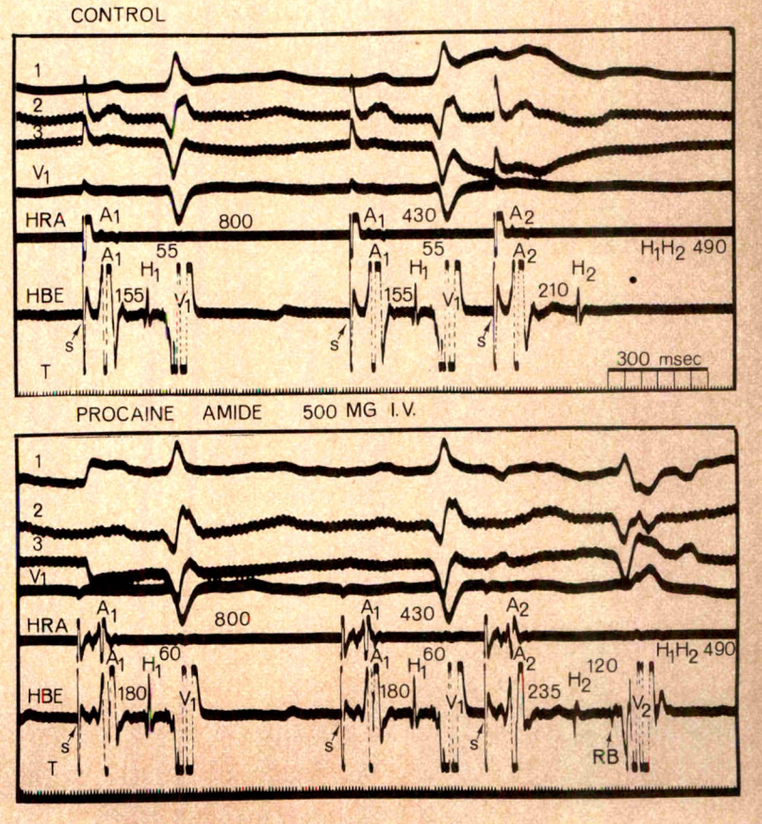

FIGURE 4. Effect of procainamide on the effective refractory period of the His-Purkinje system. The basic paced atrial cycle length is 800 msec. During control studies block occurs within the His-Purkinje system at an atrial coupling interval (A_1–A_2) of 430 msec. The critical H_1–H_2 interval determining the effective refractory period of the His-Purkinje system is 490 msec. After infusion of procainamide, at the same H_1–H_2 interval that defined the effective refractory period of the His-Purkinje system in the control period, conduction to the ventricles resumes. However, there is a marked delay between the His bundle potential and the right bundle potential (RB) of the conducted beat. This suggests that procainamide actually prolonged refractoriness in the proximal His-Purkinje system, thus allowing a more distal area of refractoriness to recover, and resulting in ventricular depolarization (see Discussion). The conduction time through the A–V node (A_1–H_1) and His-Purkinje system (H_1–V_1) of the basic drive beats was prolonged by procainamide.

TABLE III

Plasma Levels of Procainamide (mg/liter)

Case no.	End of Infusion	End of Study
1	12	7.2
2	5.8	3
3	12	10
4	7	6
5	14	4
6	14	12
7	9.6	7.2
8	16	8
9	9.4	3
10	12	*
11	13	*
12	13.2	10
13	11	5.7
14	12	4.8
15	14	*
16	14	12

* Incomplete data.

His-Purkinje system conduction and had little effect on ventricular muscle.

Previous studies[1,2,4,7,13,15,16,23,24,27,29] using microelectrode techniques and anesthetized dogs have demonstrated that procainamide prolongs the refractory periods of the atrium and His-Purkinje system. Our results are in general agreement with these findings. One apparent discrepancy occurred in one patient in whom procainamide appeared to shorten the effective refractory period of the His-Purkinje system. As shown in Figure 4, procainamide caused a marked delay in conduction between the His bundle and right bundle branch deflections. This delay probably allowed a more distal area of refractoriness to recover, thus permitting conduction to the ventricles.[33] The shortening of the effective refractory period of the A–V node was somewhat unexpected in light of the variable prolongation of A–V nodal conduction time induced by procainamide. There are three possible explanations for this somewhat unexpected result: (1) During control studies the apparent block in the A–V node was actually a block within the His bundle itself, the His deflection not being recorded because of a low density of current.[34] Procainamide, by causing delay in conduction within the A–V node, permitted the impulse to arrive at the bundle of His at a later time in the cardiac cycle when the structure was no longer refractory, and consequently A–V conduction resumed. (2) If the site of initial block was in fact within the distal A–V node, then one can postulate that, by a similar mechanism, procainamide caused delay in the proximal A–V node, thus allowing the previously refractory distal area to recover. (3) Shortening of the effective refractory period of the A–V node may be due to the antivagal effects of procainamide.[12,13,17] Because the clinical effects of procainamide depend on a balance of its direct effects (impairing conduction and prolonging refractoriness) and its indirect antivagal effects (shortening A–V nodal conduction time and refractoriness), it is conceivable that procainamide could shorten the effective refractory period of the A–V node while variably affecting A–V nodal conduction. Any one of these mechanisms may have been operative in our patients.

In our study procainamide produced a small increase in spontaneous heart rate. This is at variance with results in dogs[18,19] which showed depression of sinus rate of up to 20 percent after administration of procainamide. Clinical experience has shown that the effects of procainamide on heart rate are unpredictable.

Effect of cycle length on refractoriness: Our study confirms the results of prior microelectrode studies[35] which showed that at shortened paced cycle lengths the refractory period of the atrium and His-Purkinje system decrease. The effective refractory period of the A–V node, however, increased at shorter paced cycle lengths. This finding has been further substantiated in our laboratory.[36]

Plasma procainamide levels: Plasma levels of procainamide were in the therapeutic range[2,4,32] during our studies, and no toxic reactions were noted. Woske et al.[15] found no effects of procainamide in dogs until concentrations of 20 mg/liter were infused. The slow rate of infusion used in our study apparently allowed the volume of distribution to be reached by the end of the infusion in several patients. This explains the lack of a marked initial peak and severe toxicity when the drug is infused more rapidly.[32]

Clinical correlates: Our study reveals that the major effects of short-term infusions of procainamide were to prolong conduction and refractoriness in the His-Purkinje system. These properties suggest caution in using this agent in the presence of bundle branch block. In addition these properties may be responsible by way of a reentry mechanism for the occasional ventricular tachyarrhythmias seen after toxic doses of procainamide. These arrhythmias have previously been attributed to enhancement of automaticity.[14,16] These effects of procainamide are in contrast to the electrophysiologic properties of lidocaine[37] and diphenylhydantoin (Dilantin®)[38] in man. The latter drugs shorten the refractoriness of the His-Purkinje system and do not affect His-Purkinje system conduction and therefore they may be safer to use in the presence of intraventricular conduction disturbances. Since the effects of procainamide on A–V nodal conduction are minimal, the use of this drug in the presence of first degree A–V block or classic Mobitz type I second degree block may not be as dangerous as previously suggested. In addition, the shortening of the effective refractory period of the A–V node and lengthening of the effective refractory period of the atrium may increase the ventricular response in atrial flutter or fibrillation by decreasing concealed conduction in the A–V node.

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Arrhythmias After Cardiac Transplantation

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To determine the nature and frequency of arrhythmias that affect the denervated transplanted human heart, we examined sequential electrocardiograms in 45 of the first 47 cardiac allograft recipients at Stanford University Hospital. Atrial arrhythmias were detected in 72 percent of patients and were frequently associated with acute or chronic rejection episodes. Ventricular premature beats were noted in 57 percent of patients. Two patients had electrocardiographically documented ventricular fibrillation, and two additional patients died suddenly from presumed ventricular arrhythmias. Preliminary data indicate that these arrhythmias can be treated successfully with antiarrhythmic drugs, cardioversion or treatment of the underlying rejection process. Our experience suggests that autonomic innervation of the heart is not a prerequisite for the development of cardiac arrhythmias and is not required for response to antiarrhythmic therapy.

A unique population of patients surviving with denervated allografted hearts has resulted from the successful cardiac transplantation program at Stanford University Medical Center. As of September 1, 1972, a total of 47 patients had received cardiac allografts, and 17 had survived up to 44 months after transplantation. The functional capabilities of the denervated heart have been well described by our group and others.[1,2] In contrast, the electrophysiologic characteristics of the denervated heart are only currently undergoing analysis.[3] These studies are particularly relevant because of the high rate of observed cardiac arrhythmias after cardiac transplantation in both dogs and man. Lower et al.[4] reported that 29 (58 percent) of 50 homografted canine hearts demonstrated some form of arrhythmia during daily electrocardiographic monitoring. Most of these arrhythmias either heralded or accompanied rejection episodes.

Current theories on the genesis of cardiac arrhythmias have implicated the central and autonomic nervous systems.[5–7] Reinnervation has been reported in dogs with experimental surgical neural ablation of the heart and after cardiac transplantation.[8,9] Possible reinnervation has also been reported in the dog with an allografted heart 140 days after transplantation.[10] In contrast, there has been no evidence of autonomic reinnervation of the human cardiac allograft up to 44 months after transplantation.[1,11] In this report we describe the prevalence and type of documented arrhythmias in the denervated human heart and discuss possible alternate pathogenetic factors.

Methods

Details of the cardiac transplant program at Stanford, including donor and recipient selection, surgical technique and postoperative management, have been described elsewhere.[12] Table I lists the medications currently used in the immediate and 1 year postoperative periods. Approximately 70 percent of the patients require constant or intermittent diuretic therapy because of fluid-dependent edema. Serum potassium levels are determined at least

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weekly in these patients, with appropriate replacement. Digitalis therapy is not used in long-term patients. Electrocardiograms are recorded one to three times daily during the initial hospitalization period of 4 to 8 weeks. Each electrocardiogram is reviewed for rate, arrhythmias and QRS voltage changes to guide in the diagnosis and therapy of rejection. After the patient is discharged from the hospital, electrocardiograms are recorded once or twice weekly indefinitely. All electrocardiograms are reviewed, and additional arrhythmia documentation is obtained from bedside cardiac monitoring records. An arrhythmic episode is defined as any abnormal rhythm detected singly or recurrently within a week's time. Thus, multiple premature ventricular contractions recorded on the standard electrocardiogram daily for 5 days would be recorded as a single episode of premature ventricular contractions in the prevalence tables. In 14 long-term survivors 10 hour ambulatory electrocardiograms have been obtained on a regular basis and bicycle ergometer stress electrocardiograms have been obtained once monthly. These data are reviewed to assess the type and frequency of arrhythmias in the long-term ambulatory transplant patient. An arrhythmic episode in these studies is defined as any abnormality of rhythm occurring during the monitoring period.

Denervation Data

The presence of a residual innervated recipient atrium to which the donor heart is sutured allows comparison of innervated and denervated sinus nodal responses to cardiovascular reflexes and autonomic blocking drugs.[13] The residual innervated recipient sinus nodal rate is 70 to 80 beats/min and responds appropriately to vagal blockade produced by the intravenous administration of atropine, whereas the donor atrial rate, which actually controls the transplanted heart, shows no such response (Fig. 1). Other physiologic or pharmacologic maneuvers such as rate response to the Valsalva maneuver or transient systemic hypertension have been used to document complete denervation and the lack of reinnervation in all patients. Studies are under way to confirm histochemically the apparent complete short- and long-term autonomic denervation. It should be noted that the recipient sinus node and atrial P waves are "dissociated," as observed on the electrocardiogram, and have never been shown to control or affect the donor heart in our patients (Fig. 2).

TABLE I

Drug Therapy After Cardiac Transplantation

Medication	Average Dose (mg) in Postoperative Period	
	1 Month	1 Year
Prednisone	60	30
Azathioprine	175	175
or		
Cyclophosphamide	75	75
Coumadin®	5–10	5–10
Persantine®	400	400
Diuretic agent	As needed	As needed
Antacid agent	As needed	As needed

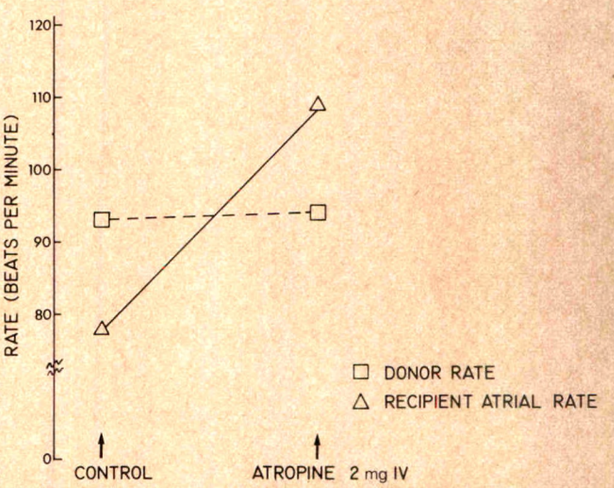

FIGURE 1. Atrial heart rates before and after intravenous administration of atropine in a patient after cardiac transplantation. Note the higher "resting, denervated" rate of the donor atrium, without response to the atropine.

Results

Table II lists the type and frequency of arrhythmias in relation to time after transplantation. The 45 patients represent a total of 37.4 years (449 months) of survival. During this period, 168 atrial, 28 junctional and 89 ventricular arrhythmic episodes were detected. There was a very high rate of atrial irregularities in the first 6 months after transplantation. Atrial arrhythmias represent 70 percent of the total arrhythmic episodes, with atrial premature contractions observed in 26 patients (52 percent) and atrial flutter in 4; six episodes occurred in the immediate postoperative period. One patient had recurring atrial bigeminy for 1 1/2 years and ultimately required a demand pacemaker for periods of sinus arrest. The most frequent junctional rhythm was premature beats in the first month postoperatively.

Ventricular arrhythmias were not unusual and were detected in 26 patients (57 percent). During intensive therapy for severe rejection, two patients had electrocardiographically documented ventricular fi-

FIGURE 2. Electrocardiogram, lead II, from a patient after cardiac transplantation. Note the constant P–R interval of the donor atrial wave with conduction to the ventricle. The P waves marked "R," representing the residual recipient's atrium, are dissociated from the QRS complexes.

TABLE II

Prevalence and Type of Arrhythmia by Time After Cardiac Transplantation*

Arrhythmia	Episodes (no.)/Patients (%) in Postoperative Period		
	0–30 Days	1–6 Months	>6 Months
APCs	22/34	58/67	30/40
Atrial flutter	6/4	2/7	2/7
Atrial fibrillation	3/6	2/7	2/7
PAT	6/11	1/3	1/7
Junctional	23/30	7/20	3/13
VPCs	15/23	25/30	43/40
Ventricular fibrillation	...	2/7	2/13
Arrhythmic Episodes/1,000 patient days (no.)			
Supraventricular	48.6	9.0	3.8
Ventricular	11.7	3.4	4.6

*See Methods for definition of arrhythmic episode.
APCs = atrial premature contractions; PAT = paroxysmal atrial tachycardia; VPCs = ventricular premature contractions

TABLE III

Arrhythmias During Submaximal Exercise Testing*

	Time After Transplantation	
	1–6 Months	>6 Months
Patients (total no.)	25	17
Studies (total no.)	36	101
Studies with APCs (no.)	3	2
Studies with VPCs (no.)	...	3
Studies with APCs and VPCs (no.)	8	9

* See Methods for definition of arrhythmic episode. Abbreviations as in Table I.

TABLE IV

Prevalence and Type of Arrhythmias Associated with Acute Rejection Episodes*

	Time After Transplantation		
	0–30 Days	1–6 Months	>6 Months
Rejection episodes			
Total no.	48	37	25
Total per 1,000 patient days	37.6	4.6	2.6
Type of arrhythmia			
Supraventricular	10	13	10
Ventricular	4	4	1

* See Methods for definition of arrhythmic episode.

brillation, responding to electrical defibrillation at 400 watt seconds. One patient subsequently died from unremitting rejection. Two long-term survivors died suddenly at home, without premonitory symptoms or chest pain. Autopsy studies of these patients, who died 33 and 45 months, respectively, after transplantation, demonstrated severe coronary atherosclerosis.

Arrhythmias during exercise testing: In the first 6 months after transplantation, 36 submaximal bicycle ergometer tests were performed (Table III). Heart rate response was slow and ranged from 110 to 140 beats/min, consistent with denervation. There was a low rate of arrhythmias in response to 10 minutes of exercise, with no obvious relation to time after transplantation. Detected arrhythmias during exercise usually consisted of an occasional premature beat (fewer than 1 in 100 beats) and were not repetitive.

Arrhythmias during tape-recorded monitoring: A total of 600 hours of tape-recorded ambulatory electrocardiographic monitoring were reviewed in 14 patients. Only three patients had no arrhythmia. Monitoring frequently documented arrhythmias not seen on supine routine electrocardiograms, but these usually consisted of only a rare premature beat, usually atrial in origin. No ventricular tachycardia or other life-threatening arrhythmias were detected.

Prevalence of Arrhythmias During Rejection

Cardiac arrhythmias frequently herald the onset of an acute rejection episode.[14] We reviewed all 110 diagnosed and treated rejection episodes in the 45 patients (Table IV) and noted a particularly high percent of rejection episodes per 1,000 patient days during the first month after transplantation. Forty-one percent of the rejection episodes were associated with arrhythmias, mostly atrial in origin.

Aggressive treatment of the associated rejection episode resulted in resolution of the arrhythmia within 1 week in 97 percent of these episodes. Antiarrhythmic drugs, including quinidine and procainamide, were used for 2 to 3 day periods to suppress a recurrent supraventricular arrhythmia until a rejection episode was controlled. Studies are presently under way to assess more carefully the effectiveness of quinidine and procainamide in denervated hearts, but both agents appear to be useful in these cases. Electrical cardioversion was successful in treating atrial fibrillation or atrial flutter in eight instances. Settings of 25 to 200 watt seconds have been used during cardioversion without causing significant postconversion arrhythmias or sinus arrest.

Discussion

We have reviewed the possible etiologic or contributing factors in the high rate of arrhythmias in patients after cardiac transplantation. Only two patients required digitalis postoperatively, and neither had an increased prevalence of arrhythmic episodes during that period. Between 80 and 90 percent of our patients required diuretic agents for treatment of fluid retention secondary to corticosteroid therapy, but neither use of these agents nor hypokalemia

could be related to the prevalence or type of arrhythmias. All patients receive potassium replacement therapy and have weekly serum potassium determinations.

Several investigators[15–17] have demonstrated sensitization to circulating catecholamines after experimental cardiac denervation. Studies are under way to determine whether this observation can be confirmed in man. The relatively low rate of arrhythmias in the long-term, nonrejecting cardiac transplant survivor at rest and during exercise suggests that such sensitization may be a contributory but not a primary mechanism. The contribution of lack of vagal tone is difficult to determine, but this factor may account for the increased propensity to arrhythmias during rejection-induced myocardial injury or its associated stress.

The 40 percent rate of occurrence of arrhythmia during a cardiac rejection episode, and the almost invariable resolution of the arrhythmia with suppression of rejection, indicates a pathogenetic relation. Pathologic studies during rejection show cellular infiltration, interstitial edema and various degrees of myocardial cell injury, with resolution of these changes on therapy. Although a definite etiologic "agent" requires further definition, one likely sequence of events is local myocardial and conductive tissue injury during rejection, with the development of arrhythmias that are perhaps aggravated by lack of vagal tone and hypersensitivity to catecholamines.

Severe coronary atherosclerosis was documented in 6 of the 12 patients who died more than 6 months after transplantation. Exercise-induced premature ventricular contractions were observed in three patients with documented coronary artery disease, two of whom died suddenly. Ischemia-induced injury or sensitization to fatal ventricular arrhythmias, or both, may have been a major factor in the sudden death of these two patients.

Hinkle et al.[18] reported that 76 percent of middle-aged men studied by a 6 hour ambulatory electrocardiographic recording had one or more supraventricular premature contractions, and 62 percent had one or more ventricular premature contractions. Less than 10 percent had more than 10 ventricular or supraventricular premature contractions per 1,000 beats. In contrast, an arrhythmic episode was defined in our report as any arrhythmia occurring *or* recurring during a week's time. Our impression is that cardiac allograft recipients have a quantitatively higher rate of recurring arrhythmias, particularly in the first 3 months after transplantation.

In conclusion, cardiac arrhythmias are common in the transplanted denervated human cardiac allograft. Local injury secondary to acute rejection may be an important pathogenetic factor. Lack of the normal "suppressant" vagal tone or hypersensitivity to catecholamines, or both, may contribute to this high prevalence rate. Preliminary observations suggest that these arrhythmias may be treated successfully with antiarrhythmic drugs, cardioversion or treatment of the underlying rejection episode. These data suggest that autonomic neural control of the heart is not necessary for production of cardiac arrhythmias, including ventricular fibrillation resulting in sudden death.

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Criteria for Electrocardiographic Differentiation of Right Ventricular Hypertrophy from True Posterior Myocardial Infarction

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Electrocardiograms recorded from patients with true posterior myocardial infarction show an abnormal anterior shift in the QRS forces. Differentiation of these records from those of right ventricular hypertrophy has been recognized as a difficult problem for a long time. An attempt was made to establish criteria for separating electrocardiograms of posterior myocardial infarction from those of right ventricular hypertrophy exhibiting a similar pattern. Frank lead electrocardiograms obtained from 81 patients with posterior myocardial infarction were compared with electrocardiograms recorded from 71 patients with right ventricular hypertrophy.

With two measurements that can be easily obtained, 70 percent of the posterior myocardial infarction records were classified correctly with 15 percent of the right ventricular hypertrophy records being misclassified. A set of three measurements for right ventricular hypertrophy correctly identified 55 percent of cases of right ventricular hypertrophy; however, 13 percent of the posterior myocardial infarction records were misclassified as right ventricular hypertrophy.

With seven measurements obtained on the basis of multivariate analysis, 78 percent of the posterior myocardial infarction and 79 percent of right ventricular hypertrophy cases were correctly classified. These measurements were found to be useful in classifying records that could not be categorized by hand measurements. Classification procedures were also tested in 23 autopsy cases with results equal to or slightly better than those obtained in clinical samples.

Several measurements on the QRS vector loop previously considered useful in the differentiation of right ventricular hypertrophy from posterior myocardial infarction gave disappointing results when tested in our samples.

Electrocardiographic and vectorcardiographic changes that occur as a result of true posterior myocardial infarction closely resemble those caused by right ventricular hypertrophy. True posterior infarction, also referred to as high posterior, strictly posterior or posterobasal infarction, involves the posterior aspect of the left ventricle just beneath the atrioventricular groove. Both posterior myocardial infarction and right ventricular hypertrophy are associated with an abnormal increase in anterior electromotive forces manifested in the Frank lead electrocardiogram by a prominent Q wave in lead Z and an abnormally increased Q/R amplitude ratio in that lead. In the 12 lead electrocardiogram an abnormally tall R wave in leads V_1 and V_2 with an R/S ratio greater than 1 occurs in true posterior myocardial infarction as well as in right ventricular hypertrophy. Differentiation of the

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two conditions from an electrocardiographic tracing when no clinical data are available is difficult and often impossible. To our knowledge there has been only one quantitative investigation performed so far with the purpose of improving the differentiation. Mathur and Levine,[1] in an attempt to search for the best discriminators between the two conditions, measured several scalar and vectorial parameters of the Frank vectorcardiogram in 203 patients with right ventricular hypertrophy and 85 patients with posterior myocardial infarction. Using three angular and one amplitude measurements, they were able to identify correctly 80 to 90 percent of the cases in each group.

In view of the importance of the differentiation of right ventricular hypertrophy from posterior myocardial infarction in clinical and epidemiologic studies, we considered that another quantitative investigation of this problem was justified. In this study we attempted to define simple criteria that could be used in day to day reading of the Frank lead electrocardiogram and to provide a separate set of criteria for differentiating the two groups by using the more complex statistical technique of multivariate analysis. We also tried to separate the two groups with use of the criteria proposed by Mathur and Levine.[1]

Material and Methods

Electrocardiograms were selected from a large library of taped records obtained during a cooperative study conducted at eight Veterans Administration hospitals. All recordings were made on frequency modulation magnetic tape, using Frank's corrected orthogonal lead system. Tracings were processed by a Control Data Corporation 3200 computer. The recording technique and computer methods have been previously described.[2]

For this study, electrocardiograms were selected on the basis of two measurements: (1) a Q/R ratio in lead Z exceeding 1.21, or (2) a Q wave amplitude in lead Z greater than 0.93 mv, or both. These measurements were previously found to be upper limits of 96th percentile ranges for normal subjects,[3] and electrocardiograms exceeding these measurements were considered to show an abnormal increase in anterior forces or a decrease in posterior forces.

Case material: From a total of 857 cases of myocardial infarction,[4] 81 were selected for study because they satisfied the criteria cited, probably as a result of a decrease in posterior forces caused by true posterior myocardial infarction. All patients had an unequivocal prior or recent history of myocardial infarction. The presence of previous infarction was confirmed by a review of records of previous hospital admissions and electrocardiograms, and serial examinations of serum enzymes such as glutamic oxaloacetic transaminase and creatine phosphokinase. Cases were not excluded from study because of electrocardiographic evidence of infarction in more than one location.

Records of patients with chronic pulmonary emphysema (843 cases) and mitral stenosis (121 cases) formed the right ventricular hypertrophy group. The clinical diagnosis of emphysema was confirmed by radiologic examination or pulmonary function tests, or both. In 77 patients with mitral stenosis the clinical diagnosis was supplemented by cardiac catheterization data. Of the total 964 records, 71 (63 with pulmonary emphysema and 8 with mitral stenosis) were found to satisfy the criteria cited. These cases were used for comparison with the cases of posterior myocardial infarction showing a similar QRS pattern. In both groups, electrocardiograms with QRS prolongation of 0.126 second or more indicating ventricular conduction defects were excluded from the study. The mean age was 58 ± 14 years for the patients with posterior myocardial infarction and 56 ± 12 years for those with right ventricular hypertrophy.

Diagnostic criteria: Two different sets of diagnostic criteria were chosen to separate the two groups of records. The first set consisted of relatively simple measurements that could easily be obtained by hand from a standard orthogonal electrocardiogram. Practically all simple scalar and vectorial measurements used in routine electrocardiographic interpretation were tested by the following method: 96th percentile ranges were computed for all of these measurements for both groups, and the number of cases in one group outside the 96th percentile range of the other was determined for each measurement. Measurements that separated the maximal number of cases of one group from the other were selected as the best criteria for discrimination between the groups.

The second set of criteria was selected strictly for multivariate analysis in which a group of measurements is used simultaneously in the form of so-called patient vectors. More than 300 different measurements comprising practically all spatial and scalar parameters that have been proposed for electrocardiographic analysis were computed originally for each record. Measurements that were potentially good discriminators between groups were identified by comparing the 96th percentile ranges in the cases of posterior myocardial infarction and right ventricular hypertrophy. With use of this method, 42 candidate measurements were found to be of use in separating the groups. Previous experience had shown, however, that too large a number of measurements leads to overly optimistic results which cannot be duplicated on new and independent case material. Cornfield[5] has suggested that this number should not exceed 1/20th of the number of cases under study. Since the total number of records in our investigation was 152, a maximum of seven measurements could be used if the resulting percentages of correct classification were to be reproducible on independent test tracings.

To reduce the 42 candidate measurements to the optimal number of 7, a sequential stepdown procedure[6] was utilized. At first, a mean vector was computed for each group with use of all 42 measurements. The measurement that contributed the least amount to the multivariate distance between the two groups was determined, then eliminated, and the discriminant function recomputed using the remaining 41 measurements. At the next stage, the least important of the 41 measurements was eliminated. This procedure was continued until the seven most important measurements were found. These seven measurements were then used to compute posterior probabilities in the manner described previously for electrocardiographic analysis at our laboratory[7]:

$$P(RVH|x) = \frac{g \cdot f\ (x|RVH)}{g \cdot f(x|RVH) + h \cdot f(x|PMI)} \qquad (1)$$

where x is the vector of 7 measurements, g is the prior probability of right ventricular hypertrophy, h is the prior probability of posterior myocardial infarction, $f(x|\ RVH)$ and $f(x|\ PMI)$ are the probability density functions of the vector x within the populations of right ventricular hypertrophy and posterior myocardial infarction, respectively.

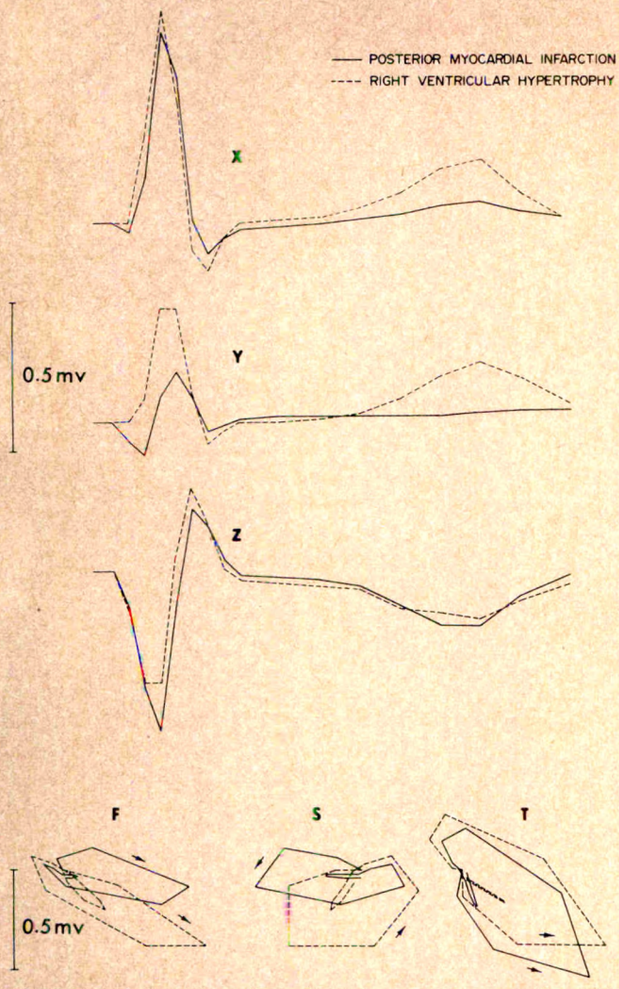

FIGURE 1. Averaged scalar leads and vector loops based on 81 records of posterior myocardial infarction and 71 records of right ventricular hypertrophy. QRS and ST–T complexes were normalized for time by dividing the duration of each into eight equal parts. Note the prominent Q wave in lead Y and the superior displacement of the initial QRS forces in the frontal and sagittal planes of the posterior myocardial infarction cases. The T loop in posterior myocardial infarction is more anterior and superior than in right ventricular hypertrophy. F = frontal; S = sagittal; T = transverse.

The posterior probability for posterior myocardial infarction is then

$$P(PMI|x) = 1 - P(RVH|x) \qquad (2)$$

Equal prior probabilities were assigned to right ventricular hypertrophy and posterior myocardial infarction in this analysis. Each individual record was classified into the category for which its posterior probability was greatest.

In addition to using the above procedure, we tried separation of the two groups by using the measurements suggested by Mathur and Levine[1] for differentiation of right ventricular hypertrophy and posterior myocardial infarction. The criteria were:

1. Direction of the mean QRS axis (half area axis) in the frontal plane.
2. Direction of the mean QRS axis (half area axis) in the transverse plane.
3. Direction of the 0.04 second instantaneous vector in the transverse plane.
4. Magnitude of the terminal rightward force.
5. Direction of inscription of the loop in the transverse plane.

The method for determining half area vectors has been described previously.[8] It should be emphasized that the measurements in the present study were made by computer from scalar Frank electrocardiographic tracings, whereas Mathur and Levine measured the different parameters visually from frontal and horizontal plane loops.

Autopsy cases: Detailed autopsy information and electrocardiograms were available for an independent sample of 449 patients. Of these, 336 had myocardial infarction at autopsy, 70 had mitral stenosis and 43 had pulmonary emphysema. From the total of 449 records, 23 were selected for analysis because they had a prominent Q wave in lead Z with an abnormal Q/R_z ratio. Of these cases, 14 had postmortem evidence of right ventricular hypertrophy with the right ventricular wall thickness exceeding 4 mm, and 8 had infarction involving the posterobasal part of the left ventricle. One patient with chronic obstructive lung disease and coronary artery disease had, at autopsy, marked right ventricular hypertrophy as well as a large posterior myocardial infarction. The 23 records were subjected to analysis by sets of measurements already obtained from the clinically diagnosed cases and were classified as showing either right ventricular hypertrophy or posterior myocardial infarction.

Frank vs. conventional electrocardiogram: Twelve lead electrocardiograms were available for comparison with results obtained on the Frank lead electrocardiogram in only a few cases. Of the 30 conventional electrocardiograms obtained in cases of myocardial infarction, only 20 satisfied the generally accepted criteria for true posterior infarction.[9] Of 17 electrocardiograms obtained in cases of right ventricular hypertrophy, only 8 had an abnormal R/S ratio in the right precordial leads. These findings suggest that in comparison with the V leads of the 12 lead electrocardiogram, the Z lead of the Frank electrocardiogram is more sensitive in recognizing an increase in anterior forces. The total number of cases manifesting abnormal anterior forces in the 12 lead electrocardiogram was too small to permit performance of any meaningful analysis to differentiate between right ventricular hypertrophy and posterior myocardial infarction.

Results

Electrocardiographic and vectorcardiographic configuration: Mean QRS and ST–T configurations of the scalar X, Y and Z leads and the vector loop projections in the frontal, left sagittal and transverse planes are shown in Figure 1. These means were derived from 81 cases of posterior myocardial infarction and 71 cases of right ventricular hypertrophy. The QRS duration and the time interval from the end of the QRS interval to the end of T wave were each normalized in time by being divided into eight equal parts. The means of each eighth were calculated and then used for drawing the averaged scalar and vector loops.

The differences between the two groups are strikingly apparent in lead Y in which the patients with posterior myocardial infarction manifest a significantly larger Q wave and an R wave that is distinctly smaller than in cases of right ventricular hypertro-

phy. The T wave amplitude in leads X and Y is considerably reduced in posterior myocardial infarction. In lead X, the S wave is more prominent in cases of right ventricular hypertrophy and the T wave more upright compared to findings in the records of posterior myocardial infarction. The averaged Z lead is similar in configuration in the two groups of records.

Differences in loop configurations correspond to their scalar counterparts. The QRS loop in posterior myocardial infarction is smaller, and its initial forces show a more superior disposition in the frontal and sagittal planes, when compared to the loop in right ventricular hypertrophy. There is some rightward displacement of the terminal part of the front plane QRS loops in right ventricular hypertrophy. Also noteworthy is the almost identical appearance of the QRS loops in the transverse plane in both groups. The rotation of the averaged QRS loops in all the three planes is similar in both groups. The T loop in posterior myocardial infarction is more superior and anterior than in right ventricular hypertrophy.

Measurements on routine orthogonal electrocardiograms: Of the several simple measurements used to separate the two groups, a Q/R ratio greater than 0.25 in lead Y proved to be the most useful. By use of this criterion, 51 percent of the cases of posterior myocardial infarction were correctly classified, but 8 percent of records in cases of right ventricular hypertrophy were misclassified as posterior myocardial infarction (Table I). The addition of a T wave measurement—namely, maximal T vector angle in the transverse plane between 90° and 180°—further increased recognition of posterior myocardial infarction to 70 percent with 15 percent of right ventricular hypertrophy cases being misclassified as posterior myocardial infarction. Only records that were not separated by the first criterion were subjected to analysis by the second to make the classification cumulative. The QRS criterion in lead Y is based on inferior wall involvement that frequently occurs in association with true posterior myocardial infarction. Use of this measurement does not permit classification of records that show an increase in anterior forces without abnormalities in the Y lead.

Several measurements were again tested in an attempt to identify the right ventricular hypertrophy records. The set of three measurements shown in Table I leads to recognition of 55 percent of the right ventricular hypertrophy records with 13 percent of the posterior myocardial infarction cases misdiagnosed as right ventricular hypertrophy. Many other scalar and vector parameters, including amplitudes, durations, angles and ST–T measurements, did not improve separation of the two groups, either because of their low sensitivity or the high rates of misclassification. Fifteen electrocardiograms (nine of posterior myocardial infarction and six of right ventricular hypertrophy) satisfied one or more criteria for both right ventricular hypertrophy and posterior myocardial infarction, and these records were not considered classifiable by the proposed measurements.

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TABLE I

Measurements for Differentiating Posterior Myocardial Infarction (PMI) from Right Ventricular Hypertrophy (RVH) on Routine Orthogonal Records

Electrocardiographic Measurement	Diagnosis Correct (cumulative %)	RVH Diagnosed as PMI (cumulative %)	PMI Diagnosed as RVH (cumulative %)
For diagnosis of PMI (81 cases)			
1. Q/R ratio in lead Y > 0.25	51	8	...
2. Maximal T angle in transverse plane 90°–180°	70	15	...
For diagnosis of RVH (71 cases)			
1. Q duration in lead Z < 0.04 sec	37	...	10
2. R/S amplitude ratio in X <1	48	...	12
3. Maximal T angle in transverse plane 270°–340°	55	...	13

TABLE II

Measurements Found Best for Multivariate Analysis, Determined by Sequential Stepdown Procedure for Differentiation Between Right Ventricular Hypertrophy (RVH) and Posterior Myocardial Infarction (PMI)

Electrocardiographic Measurements	RVH (71 cases)		PMI (81 cases)	
	Mean	SD	Mean	SD
1. 3/8 QRS_y	0.382	0.471	0.081	0.292
2. 1/8 QRS_y	−0.004	0.101	−0.060	0.084
3. R_x amplitude	0.912	0.634	0.903	0.452
4. R_z amplitude	0.456	0.526	0.314	0.099
5. Q_z amplitude	−0.596	0.324	−0.663	0.329
6. 4/8 QRS_z	0.062	0.564	−0.114	0.337
7. 7/8 QRS_z	0.010	0.150	0.036	0.071

* Measurements labeled 1/8, 2/8, and so on are amplitudes derived from time-normalized QRS complexes, obtained by dividing these complexes into eight equal parts. All measurements represent amplitudes expressed in millivolts.

SD = standard deviation.

Classification by multivariate analysis: The seven best measurements obtained for multivariate analysis are listed in Table II with means and standard deviations for each group. With use of these measurements, 78 percent of cases of posterior myocardial infarction and 79 percent of the cases of right ventricular hypertrophy were correctly classified (Table III). The error rate of classification was nearly equal for both categories.

Measurements of QRS loops: Results of classification using the criteria proposed by Mathur and

TABLE III

Results of Multivariate Classification of Cases of Posterior Myocardial Infarction and Right Ventricular Hypertrophy

	Posterior Myocardial Infarction (%)	Right Ventricular Hypertrophy (%)
Posterior myocardial infarction (81 cases)	78	22
Right ventricular hypertrophy (71 cases)	21	79

Levine[1] were disappointing. Either the rate of recognition was poor or the misclassification rates were unacceptably high. The most efficient discriminator was the direction of the mean QRS vector in the frontal plane, but only 17 percent of cases of right ventricular hypertrophy could be separated from cases of posterior myocardial infarction with the criterion suggested by these investigators. Clockwise rotation of the QRS loop in the transverse plane was observed in 20 cases (28 percent) of right ventricular hypertrophy and 14 cases (17 percent) of posterior myocardial infarction.

Autopsy data: Six of the eight cases of posterior myocardial infarction (75 percent) were correctly classified by hand measurements for posterior myocardial infarction; the hand measurements for right ventricular hypertrophy diagnosed correctly 8 of the 14 cases of right ventricular hypertrophy (57 percent). The case with combined right ventricular hypertrophy and posterior myocardial infarction satisfied hand measurements for posterior myocardial infarction. When the criteria obtained by multivariate analysis were used, the computer correctly classified 77 percent of cases of right ventricular hypertrophy and 88 percent of cases of posterior myocardial infarction. The single case that had both abnormalities was diagnosed as posterior myocardial infarction with a probability slightly higher than that for right ventricular hypertrophy. The small number of cases makes meaningful conclusions on the basis of these results difficult. However, the high percentage of correct diagnoses tends to confirm the reliability of the criteria used for classification.

Discussion

Many criteria have been proposed and used for the diagnosis of right ventricular hypertrophy in the electrocardiogram and vectorcardiogram.[10–14] Several investigators[9,15–19] have also reported on the electrocardiographic and vectorcardiographic features of posterior myocardial infarction. However, the available studies have not sufficiently stressed that differentiation of the two conditions can be difficult or even impossible in the presence of increased anterior forces.

In right ventricular hypertrophy, the initial anteriorly directed forces are usually enlarged by the increasing muscle mass of the right ventricle, which is located more anteriorly. In infarction of the posterior wall of the left ventricle, the anterior forces, being unopposed, lead to the same effect. If the right ventricular hypertrophy is sufficient to cause a marked shift of the frontal plane mean QRS axis to the right and rotate the entire QRS loop clockwise in the transverse plane, no difficulty is usually experienced in distinguishing this lesion from posterior myocardial infarction. However, moderate degrees of right ventricular hypertrophy often result in insignificant rightward deviation of the frontal plane axis and yet may shift the major part of the QRS axis anteriorly in the transverse plane without reversing the rotation. In such cases, differentiation from posterior myocardial infarction on the basis of the electrocardiogram or vectorcardiogram becomes difficult. Furthermore, since the condition of older patients is often complicated by emphysema, clinical findings may be of insufficient help in the differentiation.

The best diagnostic criteria in the Frank leads: Our data show that use of a simple QRS measurement from an orthogonal electrocardiogram permitted recognition of 51 percent of cases of posterior myocardial infarction with misclassification of 1 in 12 cases of right ventricular hypertrophy. The most useful criterion proved to be the Q/R ratio of more than 0.25 in lead Y. This ratio has been used in our laboratory for the diagnosis of posterodiaphragmatic infarction.[20] Thus, 51 percent of the cases of posterior myocardial infarction in our series had electrocardiographic evidence of inferior myocardial infarction. Since both the posterior and diaphragmatic surfaces of the heart receive their blood supply from the right coronary artery, simultaneous infarction of both areas is common, as others[15,17,19] have noted. Simple QRS measurements obtained by visual observation of an electrocardiogram fail to differentiate between right ventricular hypertrophy and posterior myocardial infarction when there is no evidence of associated involvement of the inferior wall in the latter.

In posterior infarction the T loop tends to be directed anteriorly especially in cases of acute infarction. With increasing right ventricular hypertrophy, the T loop is displaced posteriorly. The use of a single angular measurement of the T loop improved separation of cases of posterior myocardial infarction from cases of right ventricular hypertrophy. However, measurements based on the T loop are less reliable than QRS criteria, and the results may not always be reproducible in independent test samples.

The use of criteria for right ventricular hypertrophy permitted diagnosis of 55 percent of all cases of right ventricular hypertrophy with the misclassification of 13 percent of cases of posterior myocardial infarction as right ventricular hypertrophy. This classification rate is poor, but this was the best separation that could be obtained after testing several criteria. Failure to achieve a better rate of separation only emphasizes the inherent difficulty in electrocardiographic differentiation of right ventricular hypertro-

phy from posterior myocardial infarction in the population studied.

Multivariate analysis: The use of seven measurements obtained by sequential stepdown procedure enabled us to correctly identify almost 80 percent of the cases in both groups. To confirm the reliability of the results of multivariate analysis, we tested these measurements in 37 of the 81 cases of posterior myocardial infarction that we were unable to classify with use of simple QRS hand measurements. These records did not have an abnormal Q/R ratio in lead Y. Use of the computer classification method permitted correct identification of 67 percent of cases of posterior myocardial infarction. This finding confirms the high efficiency of criteria obtained by multivariate analysis in the separation of the two diagnostic categories. The high percentage of correct classification of the autopsy cases, although based on small numbers, also attests to the reliability of these criteria.

Vector loop criteria: The criteria found by Mathur and Levine[1] to be helpful in the differentiation of right ventricular hypertrophy from posterior myocardial infarction gave disappointing results when applied to our subjects. This discrepancy may be attributed to differences in the two patient groups with right ventricular hypertrophy. Their cases of right ventricular hypertrophy included several patients with congenital heart disease and mitral stenosis. Patients with pulmonary emphysema formed 14 percent of their total right ventricular hypertrophy group and 89 percent of our group.

Clinical implications: Differentiation of right ventricular hypertrophy from posterior myocardial infarction becomes clinically important only in older patients who may have coronary artery disease or pulmonary emphysema, or both. An adequate clinical history may not always be obtainable in these patients. Our study is based on adult male subjects of comparable age groups in whom clinical differentiation of right ventricular hypertrophy and posterior myocardial infarction is frequently impossible in the presence of electrocardiographic changes compatible with both conditions. We believe that our criteria will be more realistic in clinical situations in which discrimination between right ventricular hypertrophy and posterior myocardial infarction is a real problem in diagnosis.

Acknowledgment

We gratefully acknowledge the careful statistical analysis by Dr. Rosalie A. Dunn, Chief, Biostatistics and Programming Section, Veterans Administration Research Center for Cardiovascular Data Processing, and the programming assistance of Mrs. Ruby Harris and Mrs. Grace Olver.

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Comparative Prevalence of the Fourth Heart Sound in Hypertensive and Matched Normal Persons

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Occurrence of the fourth heart sound (S_4) as a physiologic phenomenon would limit its usefulness as a discriminator of disease. Reports of a high prevalence rate of S_4, as determined by auscultation and by phonocardiography in normal older persons, have provoked support and rebuttal. A blind, randomized phonocardiographic study of 50 normal and 50 age- and sex-matched hypertensive persons (mean age 53.9 ± 6.6 years) drawn from an outpatient screening clinic showed a high and virtually equal prevalence of S_4 (35 instances in each group) or possible S_4 (3 and 5 cases, respectively). It appears that in middle-aged persons, as in older persons, there is a high and equal prevalence rate of S_4. Quantitative studies appear to be indicated to determine when this sound can be considered a presystolic gallop.

Auscultatory or graphic evidence of a distinct "atrial," or fourth, heart sound (S_4) has been uniformly considered a sign of ventricular abnormality.[1–4] Recently, this view was challenged in epidemiologic studies utilizing controlled protocols. These demonstrated in both normal and abnormal older subjects a 70 to 75 percent prevalence rate of S_4, as determined by blind auscultation plus phonocardiography[5,6] and also, in larger groups, by blindly interpreted phonocardiograms.[7,8] This unexpectedly high and unexpectedly equal prevalence rate is indirectly supported by the laboratory studies of other investigators[9] and by certain clinical experience.[10] Moreover, the occurrence of S_4 as a normal phenomenon in older persons appears to explain the finding in aortic stenosis that the presence of an S_4 correlates reliably with the severity of the lesion up to age 40 but thereafter is lost as a discriminator.[11]

The elaborately blinded protocols of the epidemiologic S_4 investigations[5–8] should have eliminated bias in the results. These studies demonstrated that the auscultators were not deceived by the relative amplitude of S_4 (S_4/S_1 ratio), by phonocardiographically split high frequency components of the first heart sound (S_1) or by a large low frequency component of S_1.[5,6] Any subaudible presystolic pulsations should have been eliminated or sharply attenuated by the frequency range utilized (35 to 70 Hz). Moreover, the microphone in these studies was positioned between the apex and the left sternal border to avoid the low frequency vibrations corresponding to chest wall displacement during the apical *A* wave.[12] Nevertheless, although no other blind investigations have been reported, the common finding of S_4 as a physiologic event has been both challenged[4,13] and supported[10] by expert observers in carefully reasoned, authoritative analyses of experience with this phenomenon and its auscultatory and graphic documentation.

Because of the controversy and the evident importance of the issue of the "atrial" sound as a sign of cardiac abnormality, we investigated the phonocardiographic prevalence of S_4 in a different, somewhat younger, patient population using different technical equipment (al-

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This study was supported by a grant from the John Hancock Mutual Life Insurance Company, Boston, Mass. Manuscript accepted October 24, 1973.

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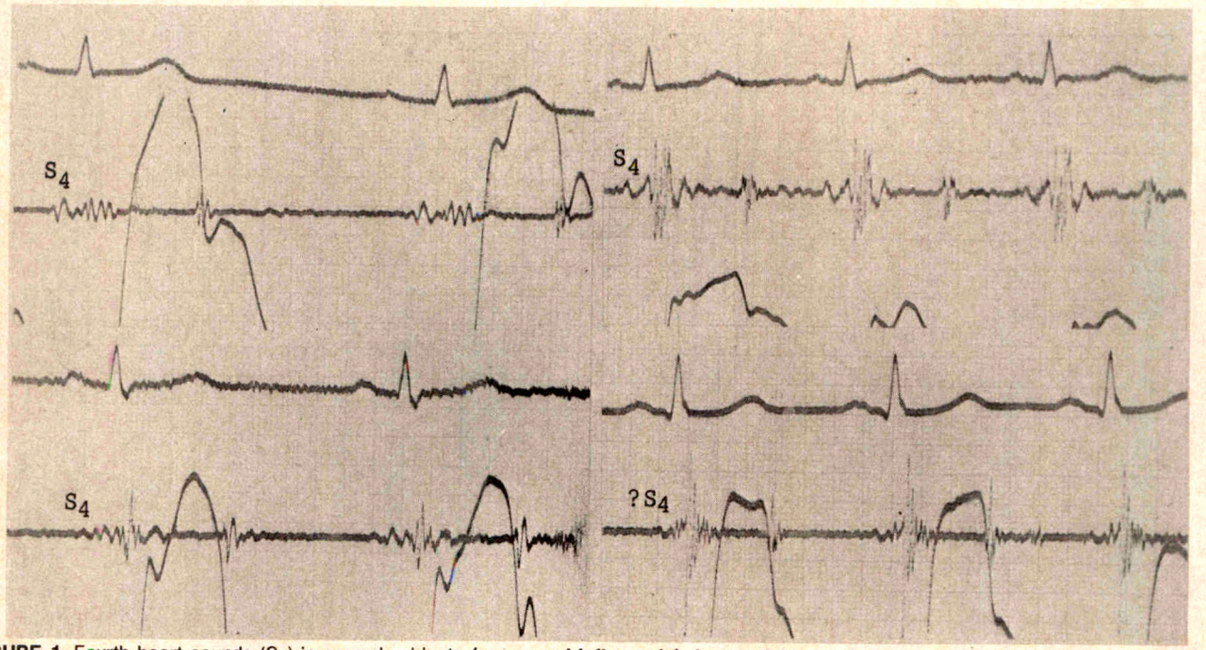

FIGURE 1. Fourth heart sounds (S_4) in normal subjects **(upper and left panels). Lower right panel** shows a vibration scored as "maybe" S_4 ($?S_4$). In each panel, **from top to bottom:** electrocardiographic lead II, phonocardiogram (70 Hz) and summits of the right carotid displacement pulse.

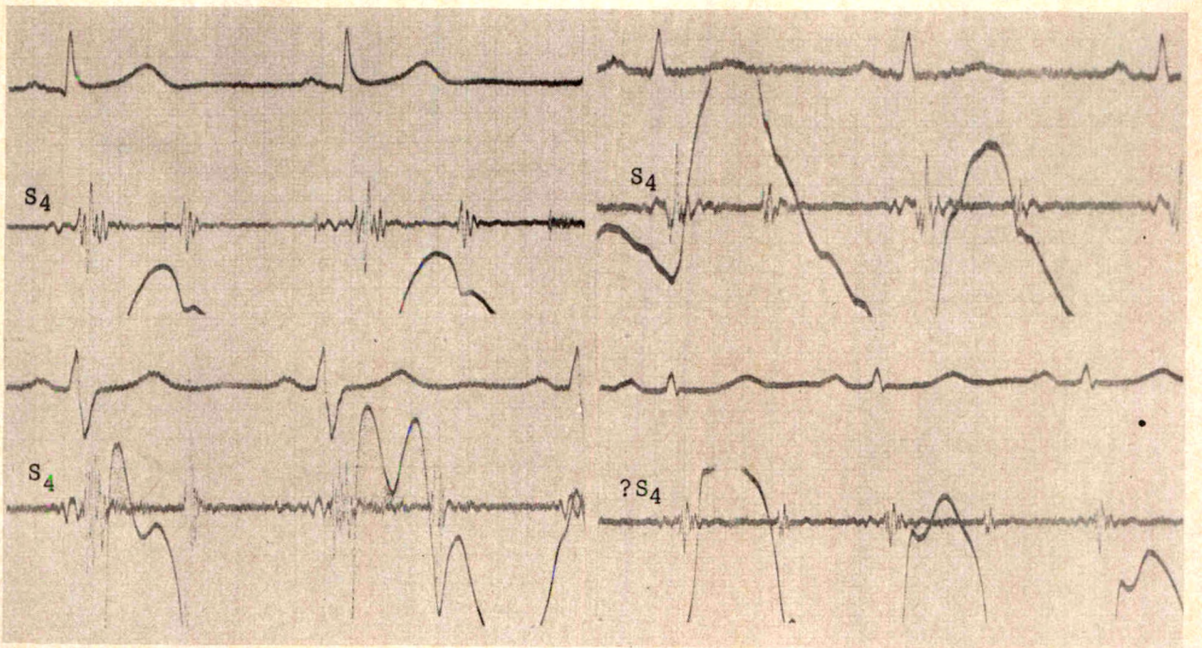

FIGURE 2. Fourth heart sounds (S_4) in hypertensive subjects **(upper and left lower panels). Lower right panel** shows vibration scored as "maybe" ($?S_4$). In each panel, **from top to bottom:** electrocardiographic lead II, phonocardiogram (70 Hz) and summits of the right carotid displacement pulse.

though in the same filter range) and a different protocol for assigning patients but equally stringent blinding of observers. The previous investigations covered from 122 to 250 consecutively studied 50 to 80 year old normal persons and patients with a variety of cardiovascular disorders.[5–8] This investigation involves 41 to 65 year old normal persons matched by sex and age with ambulatory hypertensive subjects. The ambulatory status of both groups implies better cardiovascular function than in hospitalized groups (and thus a reduced prevalence of abnormal heart sounds). Hypertensive subjects were studied because this group is expected to have a high prevalence rate of S_4.[10,14,15]

TABLE I

Prevalence of S_4 in 50 Middle-Aged Normal Persons and 50 Matched Hypertensive Subjects

Subjects	Mean Age (yr) ± Standard Deviation	S_4 Present	?	Absent
Normal				
Male	53.4 ± 6.68	16	2	7
Female	54.2 ± 6.48	19	1	5
Total	...	35	3	12
Hypertensive				
Male	53.5 ± 6.83	19	1	5
Female	54.3 ± 6.50	16	4	5
Total	...	35	5	10

Material and Methods

We investigated 100 subjects aged 41 to 65 years drawn from 530 consecutively recorded individuals on a predetermined basis: After exclusion of patients with evidence of myocardial or valvular disease, 50 patients with sinus rhythm whose brachial arterial pressure was 150/90 mm Hg or greater were matched by sex and by age with an equal number of normotensive subjects who had no evidence of cardiovascular abnormality by history, physical examination, 12 lead electrocardiogram or chest roentgenogram. Phonocardiograms were registered on a Siemens (Elema-Schönander) Cardirex recorder in the filter ranges 35 and 70 Hz, using an EMT 25B microphone that was positioned well away from the apex (between the apex and the left sternal border but somewhat closer to the latter).

No clinical data were revealed until all phonocardiograms were studied in random order and all results tabulated. S_4 was defined as distinct low frequency vibrations consistently following every P wave and preceding the QRS complex of the electrocardiogram (Fig. 1 and 2). Thus, phonocardiograms were scored "S_4–yes," "no" or "maybe" without knowledge of the patient's status. (Because of thicker base lines the "maybe" category was included for less distinct vibrations). The diagnostic data were independently scored "yes" or "no" for hypertension without knowledge of the phonocardiographic data. The results were then matched.

Results

Table I summarizes the results. When the blinding code was broken, 35 (70 percent) of the 50 hypertensive patients and the identical proportion of the 50 normal subjects had scores of "S_4–yes." Phonocardiograms in five hypertensive and three normal subjects were judged as "S_4–maybe" (Fig. 1 and 2). Insignificant sex differences are apparent in the table. The mean age for all subjects was 53.9 ± 6.62 years.

Discussion

The presence of S_4 in at least 70 percent of this normal group and the matched hypertensive patients confirms previous data showing comparable and equal prevalence of S_4 in a somewhat older (50 to 80 years) population of normal subjects and patients with mixed (mainly coronary) cardiovascular abnormalities.[5–8] Registration of S_4 by phonocardiogram does not prove its audibility. Yet the exact significance of the audible S_4 in older persons has also been questioned[5,6,9,10] although there is general agreement that a very loud "atrial" sound correlates well with ventricular overloading.[4,10] (The exact loudness of this sound would be a subject for quantitative studies: If the mere presence of S_4 can be normal in older persons, when does it become a presystolic gallop?). In this investigation, care was taken to ensure elimination or attenuation of low frequency precordial movements associated with the presystolic left ventricular *A* wave by placing the microphone well away from the apex, keeping the patient supine (thus avoiding the left lateral decubitus) and utilizing a low frequency filter cutoff of 35 Hz. We did not record an apex cardiogram[16] because (1) the criteria used to identify the timing of S_4 have proved sufficient[5,8,10] (that is, no other event is being registered), and (2) the *A* wave of the apex cardiogram merely indicates a presystolic precordial movement approximately synchronous with a left ventricular S_4.

The results of our study suggest that (1) S_4 is as common in middle age as it is in old age, and therefore its presence is not in itself a sign of cardiovascular abnormality; and (2) phonocardiographic and further auscultatory studies of S_4 may be desirable to elucidate any quantitative characteristics that distinguish the S_4 gallop from the normal S_4.

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Sinus Nodal Reentry

Effect of Quinidine

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The recently developed experimental model for sinus nodal reentry was used to assess the effect of quinidine in 20 dogs. Sinus nodal reentry was demonstrated in 19 dogs and was abolished in all dogs when plasma levels of quinidine (average 4.8 mg/liter) were in the therapeutic range after an average infusion time of 7 minutes. Characteristically in 15 dogs, quinidine increased atrial refractoriness and slowed atrial conduction so that the arrival time of the atrial premature beat (A_2) in the region of the sinus node fell outside the reentry zone and sinus nodal reentry was terminated. Conduction delay along the reentrant pathway preceded loss of sinus nodal reentry in 6 of these 15 dogs, thereby suggesting that quinidine-induced conduction delay and block along the reentrant pathway may be another mechanism for abolishing sinus nodal reentry. In the four remaining dogs in which sinus nodal reentry was abolished when the premature beat continued to fall within the reentry zone, the latter mechanism seems likely.

An experimental model for demonstrating sinus nodal reentry in the dog has recently been developed in our laboratory.[1,2] In this model a closely coupled premature atrial beat, A_2, introduced at either the tip of the right or left atrial appendage or the coronary sinus region is followed within 100 to 300 msec by an accelerated beat, A_3, that is consistent with a sinus nodal reentrant beat for the following reasons: (1) Both the atrial activation sequence and P wave configuration of A_3 and the spontaneous sinus beats are similar; (2) the occurrence of A_3 is dependent upon the arrival time of excitation of A_2 in the sinus nodal region and is *independent* of the atrial site at which A_2 is introduced; (3) A_3 can be clearly distinguished from reentry in the region of the atrioventricular (A–V) node or at the site of stimulation and, also, from sinus nodal entrance block; and (4) clamping the region of the sinus node or relatively strong vagal stimulation consistently prevents the early appearance of A_3, presumably by blocking the reentrant pathway. Somewhat similar findings on sinus nodal reentry have been reported recently by Childers et al.[3]

Because sinus nodal reentry may be the basis for some atrial tachyarrhythmias in man,[4,5] in this study we examined the effect of a commonly used antiarrhythmic drug, quinidine, on this phenomenon.

Methods

Twenty mongrel dogs weighing 9 to 23 kg were anesthetized with sodium pentobarbital, 30 mg/kg body weight intravenously. The trachea was cannulated and the animal mechanically ventilated with room air. The heart was exposed by a mid-sternal splitting incision and pericardiotomy and cradled in the pericardial sac. Both vagi were sectioned in the neck and the stellate ganglia and sympathetic chains (T_1–T_4) excised so that variability in the sinus escape time would be essentially eliminated.[2] Body temperature was monitored by a rectal temperature probe and maintained at 37 ± 1° C by an electric heating pad. Teflon®-coated bipolar plunge wire electrodes[6] were in-

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serted into the regions of the sinus node, Bachmann's bundle, coronary sinus, right atrial appendage, left atrial appendage and the low atrial septum (His bundle electrogram).

Recording and stimulating techniques have recently been described.[2] In brief, basic pacing pulses were delivered to selected atrial sites (right atrial appendage, left atrial appendage and coronary sinus) at a rate of 120 to 185/min. After every 10th basic beat (A_1), a premature beat (A_2) was introduced through the same stimulating electrodes and the atrial cycle scanned at decreasing coupling intervals (10 to 20 msec decrements of A_1–A_2) until the atrial effective refractory period was reached. For each basic cycle length the sinus nodal escape time was determined by omitting A_2 after the 10th basic beat.

Definition of Terms

A_1 = the atrial depolarization of a basic atrial beat.

A_2 = the atrial depolarization of an induced atrial premature beat.

A_3, A_4, A_5 . . . = subsequent atrial beats.

A_1–A_1 = the atrial interval measured during atrial pacing.

A_1–A_2 = the coupling interval measured from the last paced beat (A_1) to the induced atrial premature beat (A_2).

A_2–A_3 = the interval measured from the induced atrial premature beat (A_2) to the subsequent atrial beat, A_3.

A_1–A_3 = the sum of the A_1–A_2 and A_2–A_3 intervals.

A_3–A_4, A_4–A_5 . . . = the intervals between atrial depolarizations subsequent to A_3.

All atrial intervals were measured from the electrogram recorded in the region of the sinus node unless otherwise stated.

S_1 = the basic beat stimulus.

S_2 = the premature beat stimulus.

Functional refractory period of the atrium = the shortest A_1–A_2 interval measured in the sinus nodal region when S_1 and S_2 are applied to a distant atrial site (right atrial appendage, left atrial appendage or coronary sinus). The functional refractory period measured in this manner is a function of the arrival time of premature atrial excitation in the sinus nodal region and is related to both atrial conduction velocity and refractoriness.

Relative refractory period of the atrium = the S_1–S_2 interval at which the delay between S_2 and the response in the sinus nodal region increases over that for the basic drive. This occurs when the S_1–S_2 interval becomes less than the A_1–A_2 interval measured in the sinus nodal region.

Effective refractory period of the atrium = the S_1–S_2 interval at which S_2 no longer is followed by a propagated atrial response.

Conduction time (CT) = the interval between activation of the left atrial appendage electrogram during left atrial appendage pacing (or right atrial appendage electrogram during right atrial appendage pacing) and the sinus nodal electrogram. CT_1 and CT_2 refer to conduction time for basic and premature beats, respectively. CT_2 after quinidine is calculated for the earliest A_2 that can be recorded in either the right or left atrial appendage. CT_2 before and after quinidine is measured for the same A_1–A_2 interval recorded at the stimulation site and at the same basic pacing rate.

Protocol

After stable sinus nodal reentry was demonstrated in 19 dogs and control electrophysiologic data were obtained, a control blood sample was collected. Quinidine gluconate was then infused intravenously at an average rate of 0.6 mg/kg per min (range 0.5 to 0.7 mg/kg per min) using a constant rate infusion pump until sinus nodal reentry was abolished. The infusion was then discontinued and a blood sample collected; postinfusion electrophysiologic data were then recorded. Another blood sample was collected when sinus nodal reentry reappeared (14 dogs). Plasma quinidine

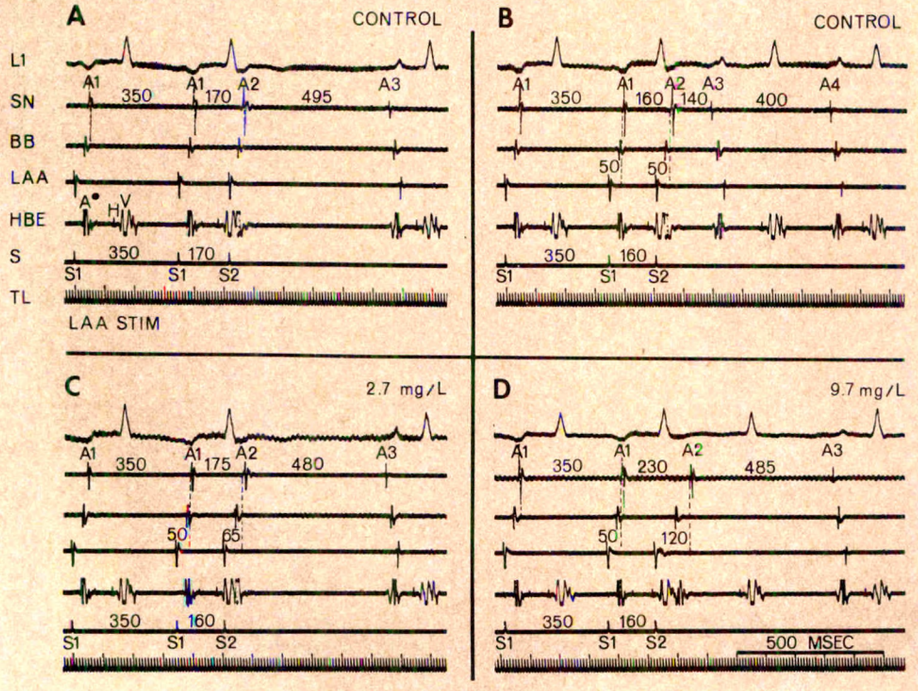

FIGURE 1. Sinus nodal reentry **(B)** during stimulation (STIM) of the left atrial appendage (LAA) and its abolition by quinidine **(C** and **D).** BB = Bachmann's bundle; HBE = His bundle electrogram recorded from the low atrial septum; L1 = standard lead I; S = stimulus for the basic (S_1) and premature (S_2) beats; SN = sinus nodal region; TL = time lines recorded at 10 and 100 msec intervals. The rapid deflections are retouched in this and the subsequent figure for the purpose of reproduction. See text.

was assayed by the photofluorometric method of Cramer and Isaksson.[7]

Results

Group A: Sinus nodal reentry could be demonstrated in 19 of the 20 dogs before quinidine. After an average infusion time of 7 minutes, quinidine abolished sinus nodal reentry in all 19 dogs. Characteristically in 15 dogs (Group A), quinidine increased atrial refractoriness and slowed atrial conduction so that the arrival time of excitation in the region of the sinus node was delayed. A_2 then fell outside the reentry zone* and sinus nodal reentry did not occur. A representative record is shown in Figure 1. In panels A to D basic and premature stimuli were applied to the left atrial appendage. In panel A, the S_1–S_2 and A_1–A_2 intervals were 170 msec and sinus suppression occurred. In panel B, the S_1–S_2 and A_1–A_2 intervals were 160 msec and sinus nodal reentry occurred. The conduction time from the left atrial appendage stimulating site to the sinus nodal region was 50 msec for both basic and premature beats. In panel C, the plasma quinidine concentration 5 minutes after the onset of infusion was 2.7 mg/liter. Although the S_1–S_2 interval was 160 msec, the A_1–A_2 interval had increased to 175 msec, and sinus nodal reentry was abolished. Atrial conduction time for the premature beat increased 15 msec, from 50 (panel B) to 65 (panel C), thus accounting for the increase in the A_1–A_2 interval. In panel C, A_2 arrived in the sinus nodal region outside the outer limit of the original reentry zone (160 msec, panel B) and sinus nodal reentry did not occur. In panel D, at the higher plasma quinidine level of 9.7 mg/liter the effect of quinidine on atrial conduction for the premature beat was even more evident and sinus nodal reentry remained absent. Typically, infusion of quinidine increased the outer limit of the original reentry zone by 5 to 20 msec (average 12 msec) before abolishing reentry.

In four dogs in Group A a progressive increase in the A_1–A_2 interval during quinidine infusion was associated with a progressive increase in the A_2–A_3 interval before sinus nodal reentry was abolished (Fig. 2). S_1–S_2 is 160 msec in panels A to C. During the control sinus nodal reentry (panel A), the A_1–A_2 interval of 155 in the sinus nodal region was 5 msec less than the S_1–S_2 interval of 160. This phenomenon was due to a so-called supernormal phase of intraatrial conduction for A_2 (between the left atrial appendage and sinus nodal region) as previously described.[8] Six minutes after the onset of infusion, the A_1–A_2 interval increased from 155 (panel A) to 170 msec (panel B), and the A_2–A_3 interval increased from 190 (panel A) to 290 msec (panel B). The change in the A_2–A_3 interval between panels A and B was gradual. In panel B, the A_1–A_3 interval of 460 was less than the basic drive escape time of 560 msec and confirmed that sinus nodal reentry was still present; that is, A_2 was not simply interpolated between the last basic drive beat and a normal sinus escape beat. Atrial conduction time for A_2 increased from 30 in panel A to 45 msec in panel B, thus accounting for the increased A_1–A_2 interval of 170. In panel C, after 8 minutes of infusion when the plasma quinidine level was 4.8 mg/liter, atrial conduction time for A_2 increased an additional 20 msec to 65, the A_1–A_2 interval in the sinus nodal region was 190, and sinus nodal reentry was abolished. The gradual increase in the A_2–A_3 interval and termination of sinus nodal reentry (abrupt increase in A_2–A_3) may represent progressive conduction delay and then block in the reentrant pathway.

In two dogs in Group A, the A_2–A_3 interval first increased as described (Fig. 2) but then unexpectedly returned toward control value during quinidine infusion before sinus nodal reentry was abolished. Possibly in these dogs an increasing proximal conduction delay allowed for more complete distal recovery[9] along the reentrant pathway, the net effect being a

* The reentry zone is the range of A_1–A_2 intervals measured in the sinus nodal region within which sinus nodal reentry occurs.[2] In this study the range averaged 15 msec, but occasionally was 45 to 55 msec in duration.

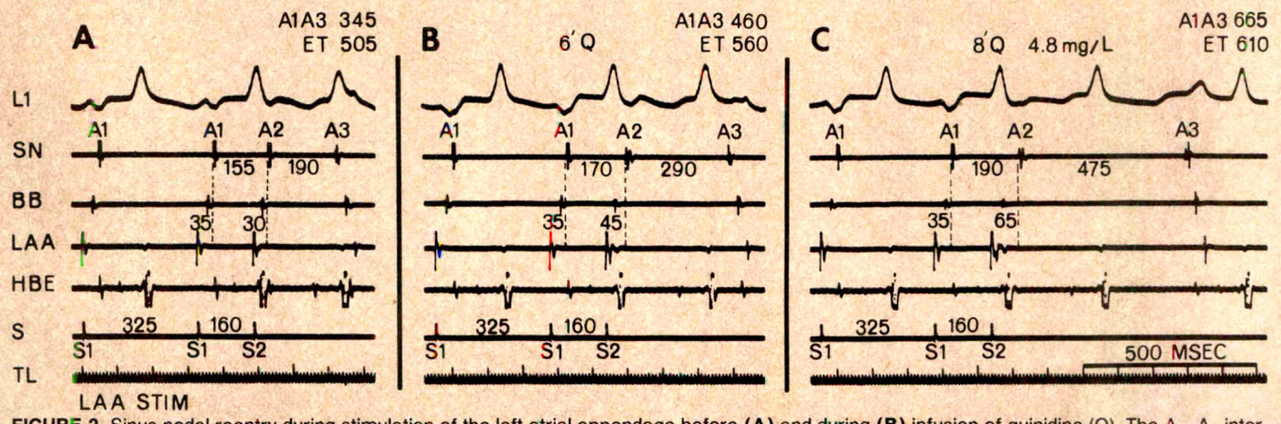

FIGURE 2. Sinus nodal reentry during stimulation of the left atrial appendage before **(A)** and during **(B)** infusion of quinidine (Q). The A_1–A_2 intervals increased **(B)** before sinus nodal reentry was abolished **(C).** See text. ET = escape time of the sinus node from the basic drive. Other abbreviations as in Figure 1.

TABLE I

Cumulative Electrophysiologic Data*

	ERP	RRP	FRP	CT_1	CT_2	A–H	H–V	QRS	Q–T	SCL
B	112 ± 3	171 ± 6	177 ± 5	34 ± 5	43 ± 5	70 ± 4	34 ± 2	55 ± 3	237 ± 6	453 ± 12
A	140 ± 6	198 ± 6	207 ± 6	40 ± 5	75 ± 6	76 ± 4	37 ± 2	61 ± 2	272 ± 9	521 ± 16
Δ	+28	+27	+30	+6	+32	+6	+3	+6	+35	+68
no.	18	19	19	15	15	19	19	19	18	18
t	7.117	7.358	8.093	2.572	8.009	2.150	3.644	4.191	6.077	6.494
P†	<0.01	<0.01	<0.01	<0.05	<0.01	<0.05	<0.01	<0.01	<0.01	<0.01

* Mean values (± standard error) in msec obtained before (B) and after (A) administration of quinidine.

† *P* values are calculated by the Student *t* test for paired data.

Δ = change; ERP, FRP, RRP = effective, functional and relative refractory periods, respectively; no. = number of dogs; SCL = sinus cycle length; for definition of other abbreviations see Methods.

decrease in the A_2–A_3 interval. Another possibility is that when quinidine suppresses phase 4 within the sinus node, conduction improves as occurs with other automatic foci.[10]

Group B: In the remaining four dogs (Group B), sinus nodal reentry was abolished during quinidine infusion although A_2 fell *within* the original reentry zone. In these dogs a change in the A_2–A_3 interval was consistently observed during quinidine infusion before sinus nodal reentry was abolished, thereby suggesting that quinidine blocked sinus nodal reentry in these dogs by its depressant effect on conduction within the reentrant pathway.

Plasma quinidine concentration: When sinus nodal reentry was abolished, plasma quinidine concentration averaged 4.8 mg/liter (range 1.7 to 10.0 mg/liter). The plasma concentration was ≤8.0 mg/liter in 18 dogs and 10.0 mg/liter in 1 dog. Sinus nodal reentry reappeared in 14 dogs after plasma quinidine concentration had decreased to an average of 2.1 mg/liter 25 minutes (average) after quinidine infusion was stopped. In 10 of these dogs sinus nodal reentry reappeared when the outer limit of the reentry zone averaged 10 msec (range 5 to 20 msec) greater than the preinfusion value.

Electrophysiologic data: Cumulative electrophysiologic data are presented in Table I. Statistically significant increases ($P < 0.05$) occurred in all variables when sinus nodal reentry was abolished. Atrial effective, relative and functional refractory periods increased 28, 27 and 30 msec, respectively. Atrial conduction time increased 6 msec (CT_1) for the basic drive beats and 32 msec (CT_2) for the premature beat. This increase in CT_2 occurred mainly because of the increase in the relative refractory period after infusion of quinidine. Thus for the same S_1–S_2 intervals before and after quinidine, A_2 was introduced earlier in the relative refractory period after quinidine and, consequently, conduction time (CT_2) was increased. A–V conduction was minimally affected by quinidine, the A–H and H–V intervals increasing 6 and 3 msec, respectively. The duration of ventricular activation and repolarization increased 6 msec (QRS interval) and 35 msec (Q–T interval), respectively. Sinus cycle length increased (sinus rate slowed) from 453 to 521 msec.

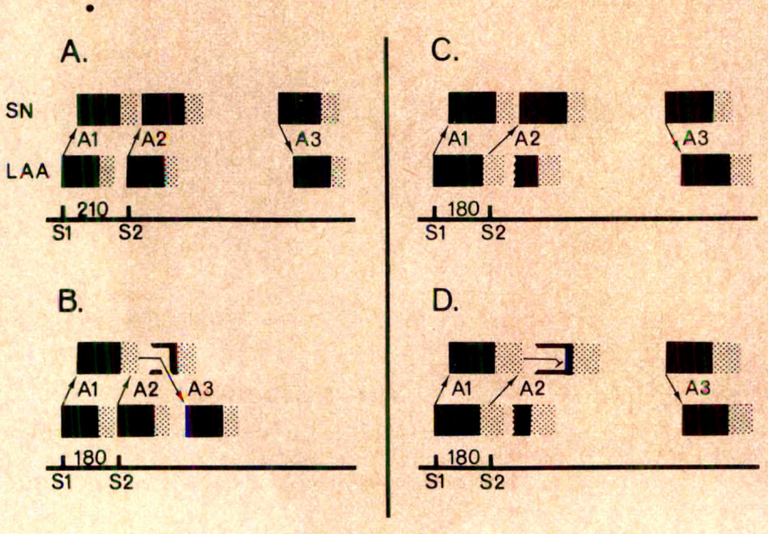

FIGURE 3. Schematic representation of conditions before administration of quinidine **(A** and **B)** and two mechanisms **(C** and **D)** that might account for the abolition of sinus nodal reentry **(B)** by quinidine. See text. Abbreviations as in Figure 1.

Hemodynamic data: When sinus nodal reentry was abolished mean arterial pressure had decreased 20 mm Hg (P <0.01) from 66 before infusion to 46 mm Hg after infusion. Preinfusion arterial hypotension resulted from opening the chest and extrinsic cardiac denervation, and occurred despite negligible (<5 cc) blood loss. Abolition of sinus nodal reentry was not considered related to a quinidine-induced decrease in arterial pressure for the following reasons: (1) in three dogs arterial pressure was restored to its preinfusion level by intravenous administration of dextran (30 to 150 cc) and sinus nodal reentry did not recur, and (2) in three dogs sinus nodal reentry was abolished when arterial pressure was unchanged from control value.

Quinidine effect when control sinus nodal reentry was absent: Sinus nodal reentry was absent before infusion of quinidine in only one dog. In this dog atrial reentry developed during quinidine infusion and appeared at times to originate from the sinus nodal region. Reentry first appeared at a toxic quinidine level of 14.0 mg/liter and was associated with an increase in the effective, relative and functional refractory periods of 60, 110 and 115 msec, respectively. The thresholds for atrial capture and conduction time were both significantly increased when compared to control values.

Discussion

The results of this study confirm our previous observations using this experimental model for the production of sinus nodal reentry and demonstrate that quinidine consistently abolished sinus nodal reentry when plasma quinidine was at a level considered to be within the therapeutic range for man.[11–14]

Schematic representation of quinidine effects on sinus nodal reentry: On the basis of the known effects of quinidine on atrial and sinoatrial tissue[10,15–20] and the results of this study, we postulate that quinidine may abolish sinus nodal reentry as schematically depicted in Figure 3. In panel A, solid and stippled rectangles correspond to effective and relative refractory periods, respectively. The total duration of refractoriness of the sinus node exceeds that of the left atrial appendage, consistent with the known disparity in refractory period duration between sinus nodal and atrial tissue.[21,22] Stimuli are applied to the left atrial appendage, and relative conduction times are depicted by arrows. When the S_1–S_2 interval is 210 msec, A_2 arrives at the sinus node outside its relative refractory period and sinus suppression occurs. A_3 represents a sinus escape beat. In panel B, at an S_1–S_2 interval of 180 msec, A_2 arrives at the sinus node within its relative refractory period and sinus nodal reentry occurs. After infusion of quinidine, atrial refractoriness is increased (panel C). As a consequence of this increase, when the S_1–S_2 interval is 180 msec, S_2 falls within relatively refractory atrial tissue and conduction time for A_2 from the left atrial appendage to the sinus nodal region is increased. If refractoriness in the sinus node is increased proportionately less than in the left atrial appendage, as shown, then A_2 will arrive at the sinus node outside its relative refractory period and sinus nodal reentry will not occur. If the S_1–S_2 interval is decreased further, the increasing latency* will prevent A_2 from arriving earlier[23] and sinus nodal reentry will remain absent. If refractoriness increases to the same degree in the sinus node and the left atrial appendage (panel D), then sinus nodal reentry will continue until conduction delay and then block occur along the reentrant pathway. The degree of change in refractoriness and conduction velocity in atrial and sinoatrial tissue during quinidine infusion determines the type of response seen.

Absence of a vagolytic effect of quinidine: Because the dogs in this study had extrinsically denervated hearts the well known vagolytic effect of quinidine[24] was not observed. Thus, the direct effect of quinidine on sinus automaticity was not opposed by the indirect vagolytic effect of quinidine, and sinus rate decreased. Presumably for the same reason, more rapid A–V nodal conduction was not observed.

Therapeutic implications: The possibility that sinus nodal reentry may be the basis for certain atrial tachyarrhythmias in man has recently been suggested.[4,5] In this study when a premature atrial beat was electrically induced, quinidine abolished the subsequent sinus nodal reentrant beat. In the absence of an induced atrial premature beat there was no sinus nodal reentrant beat. Therefore, it is reasonable to suppose that in man if sinus nodal reentrant beats (singly or in the form of a sustained tachycardia) arise after a spontaneous ectopic atrial premature beat, then quinidine might abolish sinus nodal reentry by its well known suppressive effect on ectopic atrial premature beats.[10,16] In addition, quinidine might also abolish sinus nodal reentry by delaying the arrival time at the sinus nodal region of a spontaneous ectopic atrial premature beat or by conduction block along the reentrant pathway. The last mechanism could abolish sinus nodal reentrant beats if they arise spontaneously. Of course, if sinus nodal dysfunction coexists with sinus nodal reentry then use of quinidine alone might be dangerous.

Because the effect of quinidine on sinus nodal reentry in man has not yet been reported, its effect cannot be predicted with certainty. Since vagal stimulation in the dog abolishes sinus nodal reentry,[2] the indirect vagolytic effect of quinidine in man could conceivably counteract the direct depressant effects of quinidine on sinus nodal reentry. The net effect of this interaction remains to be determined.

* In this context latency refers to the interval measured from the stimulus to the atrial electrogram recorded in the sinus nodal region.

Acknowledgment

We gratefully acknowledge the technical assistance of David Berry and Dola Thompson, the secretarial help of Anne Mazzella and the photographic services of Kenneth Donohue.

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Functional Anatomy of the Canine Left Bundle Branch

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To elucidate the architecture of the left bundle branch, activation of Purkinje (P) and myocardial (M) cells of the canine left ventricular endocardial surface was mapped in vitro before and after lesions were placed in the proximal left bundle branch. Close bipolar electrodes or microelectrodes were employed to record P and M potentials by standard techniques. The left bundle branch has conspicuous and straight border fibers that continue as bridging strands to the papillary muscles. In addition, there is a less conspicuous network of serpentine interwoven fibers in the interior of the septal portion of the bundle that has interconnections with the border fibers. Below the mid-septum and over the free wall the P fibers form a densely interwoven network. The interior septal fibers are activated nearly simultaneously with equidistant points on the border fibers. The apparent conduction velocity of the border fibers was 1.8 m/sec as opposed to 1.45 m/sec in the interior network. The bridging strands provide a shortcut across the chamber to upper portions of the free wall and septum. The pattern of activation of M cells is represented by concentric rings with an island of earliest activation (at 15 to 25 msec) in the central septum. The M cells latest to be activated are at the tips of the papillary muscles and the upper septum below the valves. Interruption of one group of border fibers may delay by 5 to 8 msec activation of P and M cells of the upper paraseptal free wall and upper septum. Lesions in the interior network delay by 2 to 4 msec activation of the P and M cells of comparatively small areas of the septum. Activation of the mid-papillary free walls, the bases of the papillary muscles and the lower septum is not affected by proximal lesions partially interrupting the bundle branch. Transection of both groups of border fibers does not produce complete block. The left bundle branch is best represented as a fan-shaped network of interwoven fibers whose diverging border fibers are specialized for rapid, distant transport.

It has become commonplace to represent the left bundle branch as a bifascicular structure.[1–4] This representation implies that the fibers of the left bundle branch are concentrated in two discrete channels before they are disseminated in the interconnected peripheral network. The left bundle branch has also been described as a "fan" or diverging network of interconnected fibers, currently a less popular description.[5] In a diverging network of interwoven fibers, small lesions should not delay activation over large regions, whereas in a bifascicular structure a small lesion interrupting a fascicle should delay activation of approximately half of the Purkinje network. Small lesions interrupting both fascicles near their origin should result in complete left bundle branch block.

To evaluate these opposing descriptions, we minutely traced the activation of the endocardial surface of the dog before and after interruption of various portions of the left bundle branch. For this pur-

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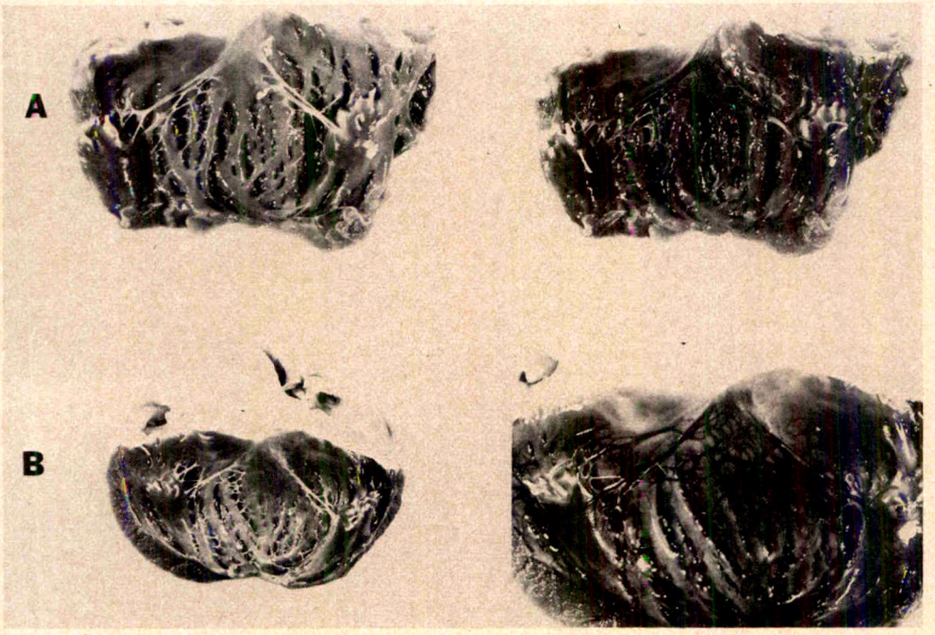

FIGURE 1. Two preparations (**A** and **B**) of the left ventricular endocardial surface unstained **(left)** and stained **(right)** with Lugol's solution. The free wall was bisected by an incision extending from base to apex. The valves and the main bundle branch are at the top, the apex at the bottom. In the unstained specimens, the relatively straight and conspicuous border fibers impart a bifascicular appearance. The interior fibers are manifest in the stained specimens.

pose we utilized recording techniques that allowed high resolution as well as discrimination between activation of Purkinje (P) and ordinary myocardial (M) cells. In other studies,[6,7] activation of subendocardial P and M cells has been mapped in some detail. However, these studies did not specifically focus on the validity of the concept of a bifascicular structure versus that of a diverging network.

Method

The entire endocardial surface of the left ventricle was included in the preparation. In 11 mongrel dogs anesthetized with pentobarbital, the heart was excised and the free wall of the left ventricle bisected by an incision extending from the base to the apex. The specimen was trimmed and pinned, endocardial surface upward, with the flaps of the bisected free wall spread flat along side the septum (Fig. 1). It was superfused with a solution held at 37°C, bubbled with 95 percent O_2 and 5 percent CO_2 and containing (in millimoles per liter): Na^+ 151.1, K^+ 4.0, Ca^{++} 1.4, Mg^{++} 2.0, Cl^- 132.3, HCO_3^- 24.0; $HPO_4^=$ 1.8 and dextrose 5.5.

Intracellular recordings were made with ultramicroelectrodes of tip resistance of 10 to 40 megohms when filled by boiling with 3M KCl. The first stage amplifier (Bioelectric NFl) had low gain (3×), high input impedance (greater than 10^{12} ohms) and negative capacitance feedback. Extracellular recordings were made with bipolar electrodes of adjacent fine, Teflon®-coated stainless steel wires (0.005 inch in diameter) led into differential amplifiers. The outputs of the preamplifiers were led into the plug-in amplifiers (Tektronix 3A74) of a dual beam oscilloscope (Tektronix 565) and photographed (Grass C4 camera). Stimulation was accomplished with a specially constructed circuit that triggered the oscilloscopic sweeps and two pulse generators (Tektronix 160 series). Radiofrequency isolation units (Bioelectric 1S2) were interposed between the pulse generators and two Teflon-coated silver wires (0.007 inch in diameter) that were in contact with the most proximal visible portion of the left bundle branch. Selective stimulation of the left bundle branch was accepted if myocardial cells closely adjacent to the bundle at the level of the stimulating electrodes were activated with a latency of at least 30 msec. The bundle was stimulated at a rate of 60/min. The activation times were essentially independent of the rate of stimulation at rates below 300/min.

A detailed drawing to scale of the preparation was made at the beginning of the experiment, and distances were measured to the nearest 100 μ with a micrometer in the eyepiece of a dissecting microscope. Each recording site was located on the drawing by means of fixed landmarks, and its distance from the stimulating electrodes was measured. For the calculation of "apparent" conduction velocity in the Purkinje system, the straight line distance from the recording to the stimulating electrodes was measured; it was recognized that this line did not necessarily indicate the true path of the impulse. In each experiment there were three fixed recording sites, two points on the anterior and posterior papillary muscles where they were joined by false chordae, and a point on the central lower septum at about the same distance from the stimulating electrode as the other two points. A fourth bipolar electrode or a microelectrode was used as a rover for detailed mapping. Incisions were made with a scalpel blade or needle tip. At least 50 separate sites on the endocardial surface were explored in each experiment. The recording sites were regularly spaced 1 to 2 mm apart over the entire surface, except in areas of the upper free walls and septum where conduction was relatively slow because Purkinje fibers were sparse. The specimens were stained with iodine (Lugol's solution) at the end of the experiment.

Results

Gross Anatomy of Left Bundle

Figure 1 shows the unstained (left side) and stained (right side) appearances of two representative specimens. In the unstained specimens, the borders of the bundle and the two groups of bridging strands to each of the papillary muscles were conspic-

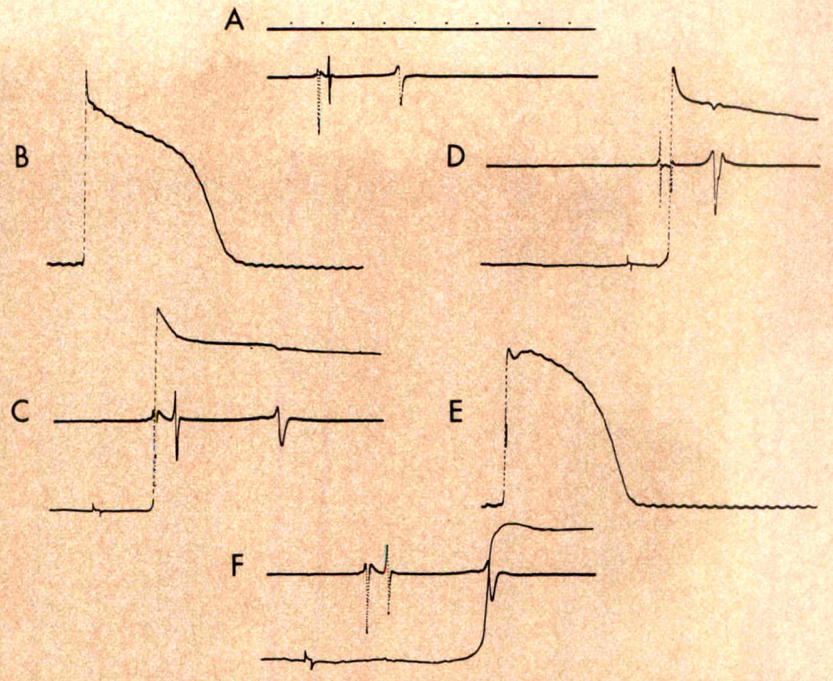

FIGURE 2. Microelectrode exploration in the immediate vicinity of a bipolar extracellular electrode. The composite electrogram recorded by the extracellular electrode **(A)** contains two early rapid components designated P deflections and a later, slower component designated M deflection. Typical P action potentials in the vicinity **(B)** had upstrokes coincident with the first **(C)** or second **(D)** rapid component of the extracellular electrogram. Typical M action potentials in the vicinity **(E)** had upstrokes coincident with the late, slower deflection **(F).** Time markings are at 10 msec intervals.

uous, imparting a bifascicular appearance. However, iodine stain invariably disclosed an interior interwoven network of serpentine fibers that had different degrees of density in different specimens. There were radial interior fibers that appeared to originate in the most proximal portion of the main left bundle branch and to connect at irregular intervals with one another and with the border fibers and the bridging strands.

The border fibers of the proximal left bundle branch pursued relatively straight paths. Approximately one fourth of the distance down the septum, border fibers departed from the endocardial surface to form free strands (false chordae) that, like suspension bridges, spanned the distance across the left ventricular cavity to the superior portions of the papillary muscles. From the points of juncture with the papillary muscles, these fibers proceeded to branch and ramify over the free walls. In many stained specimens inconspicuous fibers exterior to the prominent border fibers appeared to curl back superiorly.

Purkinje and Myocardial Cell Electrograms

P and M electrograms were usually readily distinguishable on extracellular recordings because of their different durations (Fig. 2). P electrograms were 1 to 3 msec in duration, whereas M electrograms were 6 to 10 msec in duration. Extracellular potentials attributed to P or M cells could be and frequently were verified by intracellular exploration in the vicinity of the extracellular electrodes. Verification by intracellular recording was used most often at sites where P and M deflections were close and the distinction between them was unclear (tracings 3 and 7, Fig. 3). The tracings in Figure 2 show microelectrode explo-

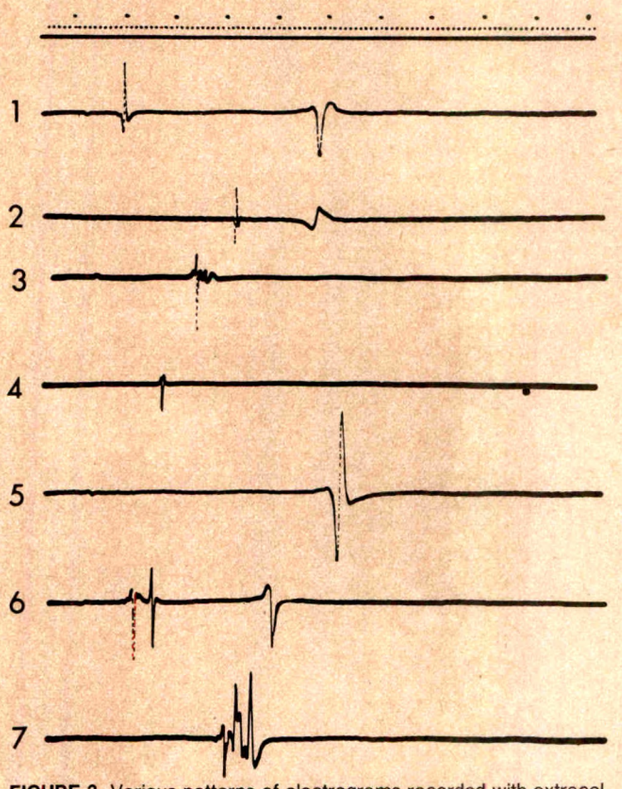

FIGURE 3. Various patterns of electrograms recorded with extracellular bipolar electrodes at different sites on the left ventricular endocardial surface. See text for description. Time markings are at intervals of 1 and 10 msec.

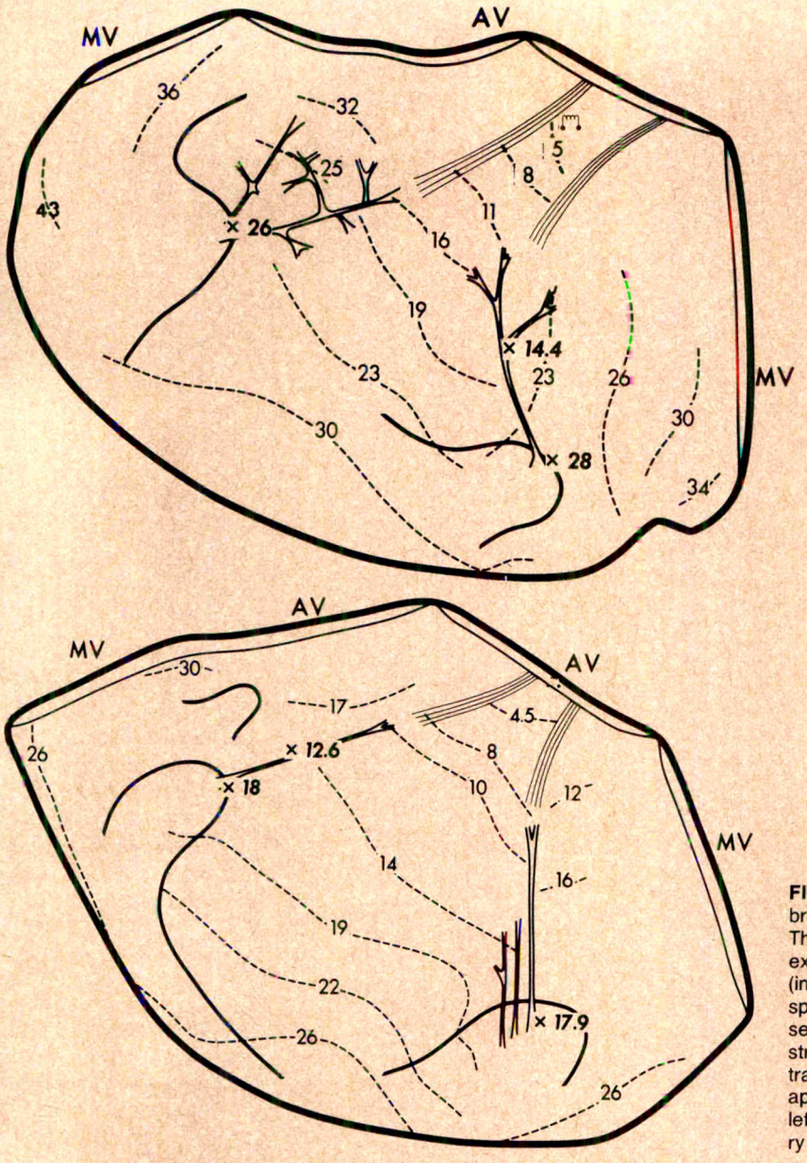

FIGURE 4. Sequences of activation of the left bundle branch Purkinje fiber (P) network in two preparations. The **dashed lines** are isochronous lines constructed exclusive of the bridging strands. The activation times (in msec) after stimulation are shown along the corresponding dashed lines. The **figures in bold type** represent activation times at sites (X) along the bridging strands and border fibers. The split aortic (AV) and mitral (MV) valves are at the top of the figure and the apex of the heart is at the bottom. The borders of the left bundle branch, the bridging strands and the papillary muscles are shown schematically.

ration in the vicinity of the bipolar electrode that recorded a composite electrogram. The first two rapid deflections in the top extracellular recording (panel A) were attributed to P cells and the third, slower deflection to M cells. Intracellular recordings in the vicinity disclosed characteristic P action potentials (panel B) with upstrokes that were coincident with either the first (panel C) or second (panel D) deflection of the electrogram but not the third. Characteristic M action potentials (panel E) were found with upstrokes coincident with the third deflection (panel F) but not the first or second. The mean maximal upstroke velocity of Purkinje fibers in these preparations was 485 ± 28 (standard deviation) v/sec.

A sample of the various patterns of electrograms encountered is illustrated in Figure 3. Tracing 1 is typical of patterns recorded near the proximal left bundle branch where P cells are activated early but underlying M cells are activated quite late. Tracing 2 is the type recorded more distally but still proximal to sites downstream where electrical continuity between P and M cells is established. Such recordings were typically obtained on the distal portions of the papillary muscles or the middle third of the septum. Tracings 3 and 7 are representative of recordings obtained at sites where electrical continuity between P amd M cells occurs. In tracing 3 the P electrogram is most prominent, and slow muscle electrograms immediately follow. In tracing 7 prominent P and M electrograms closely abut, and the distinction between them is less clear. Tracing 4 shows a pure P electrogram obtainable over bridging strands (false chordae); tracing 5 shows a pure M electrogram obtained over the upper septum outside the borders of

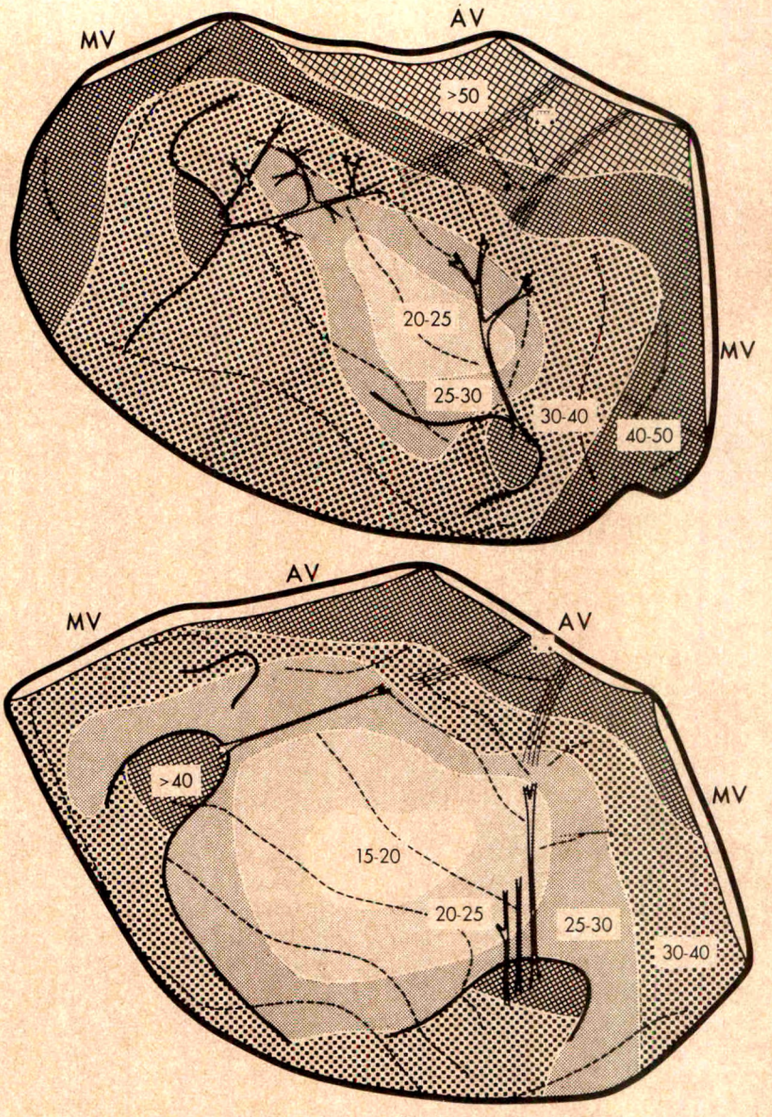

FIGURE 5. Sequential activation of subendocardial left ventricular M cells in two preparations. The corresponding sequences of P activation in the same preparations were shown in Figure 4. The numbers represent the activation times (in msec) encompassed in the areas demarcated. See legend to Figure 4.

the left bundle branch. Tracing 6 shows multiple P spikes, a pattern frequently recorded on the septum where the bridging strands originate.

The resolution of the bipolar extracellular electrode was assessed by recording electrograms with the tips of the electrodes gently touching the strand and at various distances from the strand. The amplitude of the electrogram was reduced approximately exponentially to half value at a distance of 125 μ from the strand. Comparable findings were reported in another study[8] in which similar electrodes were used. Thus, it is unlikely that activity arising more than 0.5 mm from the electrode was analyzed on the electrograms. Potentials generated by fibers at this distance from the electrodes would be reduced to about 6 percent of their value, and they would be overshadowed by potentials generated by tissues just below the recording electrodes.

Activation times of P fibers: Isochronous lines describing the wave front of activation of P cells in the left bundle branch formed arcs with slight or no central indentations. The border fibers and bridging strands were activated slightly before points in the interior network equidistant to the stimulating electrodes, but the difference was not more than a few milliseconds. Two representative samples of activation of the P fibers of the left bundle branch are depicted by means of isochronous lines in Figure 4. These isochronous lines were constructed *exclusive* of points on the bridging strands. Apparent conduction velocities for P activation could be calculated from each of the many recording sites since each site was a datum point associated with a time and a distance from the stimulating electrodes. In each experiment mean values were calculated from 5 to 10 points along each set of border fibers and from 10 to 20

points at various distances within the interior network. Calculated from seven preparations, the mean apparent conduction velocity in the interior network was 1.43 ± 0.09 (mean ± standard error) m/sec, whereas the apparent conduction velocity along the relatively straight border fibers and bridging strands was 1.73 ± 0.09 m/sec. Analyzed separately, the bridging strands themselves had a higher mean conduction velocity—2.09 ± 0.08 m/sec. The values are all significantly different from one another ($P < 0.02$). Activation of the fibers exterior to the border fibers was later than equidistant points in the interior. The exterior fibers often appeared to turn back upward (Fig. 4). The upper septum outside the borders of the left bundle branch contained no P fibers. P fibers were relatively sparse in the uppermost portions of the free walls and the distal portions of the papillary muscles; they were most abundant in the lower half of the septum and the free wall between the papillary muscles. In these areas P and M electrograms were closely adjacent (within 3 msec). Although a lacework of pale interweaving P strands was visible in these areas, even in the pinker islands between the strands P potentials often were obtained. With the microelectrode it was found that the first one to three layers had action potentials characteristic of P cells (or transitional cells), covering the lower septum and much of the lower free walls like a sheet. The total time required for P activation of the left ventricular endocardial surface was 30 to 45 msec. P activation continued for 15 to 20 msec after M activation had begun.

Activation times of M cells: The activation of M cells had a different pattern, dependent both on the pattern of P activation and on the areas where electrical continuity between P and M cells occurred. P and M continuity did not occur in the upper septum and upper halves of the papillary muscles. Two representative experiments are illustrated in Figure 5, top and bottom, which corresponds to Figure 4, top and bottom, depicting the P activation in the same preparations. Initial M activation appeared as an island in the central septum, usually in the middle third. It began 15 to 25 msec (mean 21 msec) after stimulation. The activation pattern was in the form of concentric bands around this island. The concentric bands do not represent actual conduction pathways, since the pattern of M activation is influenced by P conduction pathways as well as M conduction pathways. M cells of the papillary muscle were activated from base to apex. The last M cells to be activated were on the distal papillary muscles and the upper portion of the septum. In these areas the impulse was spread entirely by M conduction. Activation of the last M cells occurred 50 to 70 msec (mean 59 msec) after the stimulus. Activation of all M cells required 30 to 50 msec (mean 38 msec).

Effect of incisional interruption of left bundle branch fibers: The anterior or posterior border fibers were transected with transverse incisions, 3 to 6 mm long, placed about midway between the origin of the main left bundle branch and the origin of the bridging strands. Incisions interrupting less than 30 percent of the width of the left bundle branch did not produce changes in distal activation exceeding 2 msec in any of five experiments. Incisions that interrupted 30 to 60 percent of the left bundle branch resulted in delay over an area that included the upper portion of the papillary muscle, the upper portion of the paraseptal free wall and a part of the upper septum external to the main left bundle branch. Delay never occurred in more than a third (mean 27 percent) of the endocardial surface in any experiment. The maximal delay within this area was 5 to 8 msec (mean 6.8). Figure 6 shows the results of one of eight such experiments. In each of these experiments P and M cells within the area of delay were delayed proportionately. The magnitude of the delay decreased near the borders of the delayed area.

Transection of the border fibers of both sides of the left bundle branch did not produce complete heart block as long as there was a small isthmus of intact endocardium between the incisions. Figure 7 shows data from an experiment in which an isthmus of 1 mm remained between two incisions extending inward from the borders of the left bundle branch. Nonetheless activation of distal sites occurred. The distal bundle was not activated by a narrow isthmus in only one of eight experiments. In this single experiment iodine staining failed to disclose P strands within the isthmus. In the other seven experiments the isthmus contained intact P strands (interior fibers) that preserved conduction.

In six experiments the interior fibers were transected with incisions 4 to 8 mm long. There was delay of approximately 2 to 5 msec (mean 3.3 msec) in the area of the septum just distal to the incisions. The

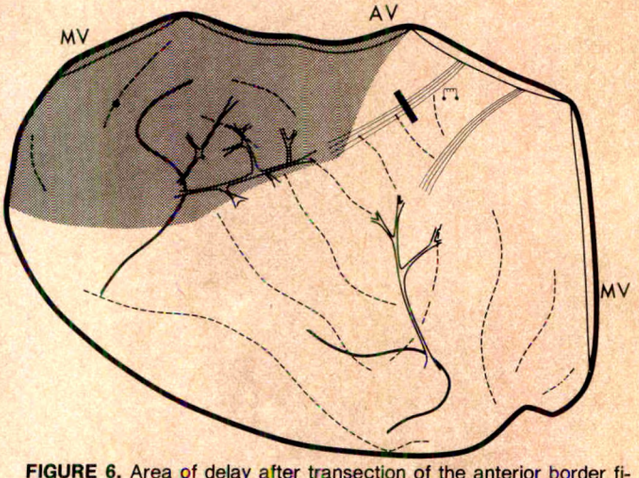

FIGURE 6. Area of delay after transection of the anterior border fibers. The incision was placed about midway between the origin of the bundle and the takeoff of the bridging strand and extended for about 40 percent of the visible width of the bundle. In the **shaded area** P and M potentials were delayed a maximum of 7 msec after the transection. See legend to Figure 4.

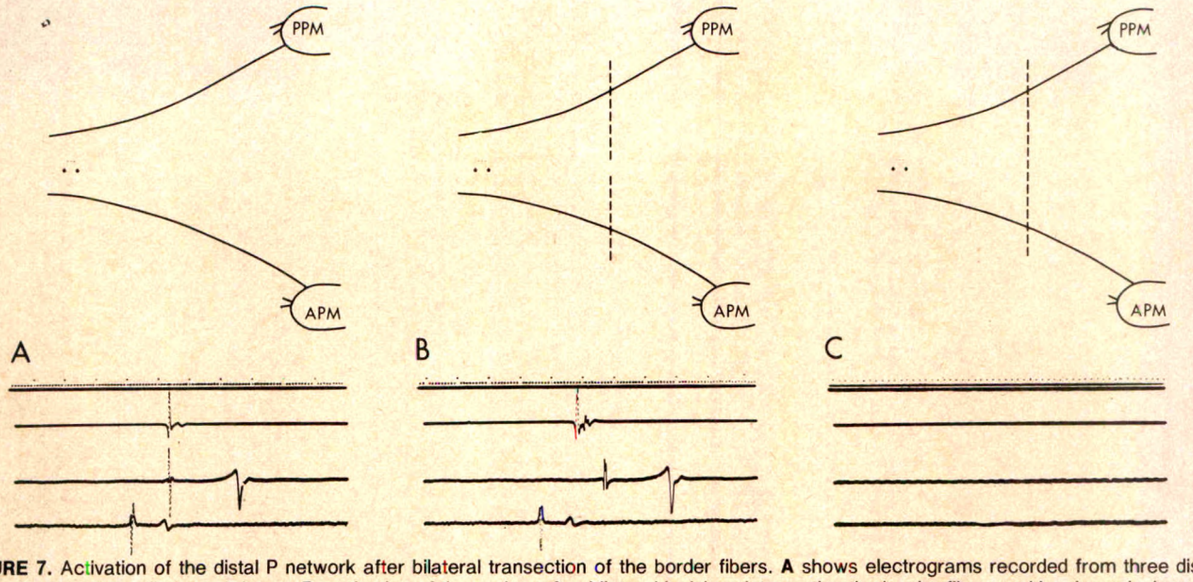

FIGURE 7. Activation of the distal P network after bilateral transection of the border fibers. **A** shows electrograms recorded from three distal sites with the left bundle branch intact. **B,** activation of these sites after bilateral incisions interrupting the border fibers and leaving only 1 mm of intact endocardium in the center of the bundle. Although the sequence of activation and configuration of the electrogram was changed, complete block did not occur. **C,** complete block after the two incisions were joined. Time markings are at intervals of 1 and 10 msec in **A** and **B** and 10 msec in **C.** The left bundle branch is schematically represented at top. APM and PPM designate the anterior and posterior papillary muscles, respectively. The incisions are represented by **dashed lines.**

area of delay was relatively small compared with the area of delay after border incisions. It was not more than one fifth (mean 12 percent) of the total area of the left ventricular endocardial surface in any experiment. A representative experiment is illustrated in Figure 8.

Discussion

Possible sources of error in methodology: The methods used in these experiments allowed detailed and discriminate mapping of Purkinje and myocardial activation of the entire left ventricular endocardial surface. Nevertheless, there were limitations and sources of error. The incision opening the ventricle necessarily interrupted fibers in the left bundle branch system. The location and direction of the incisions should have minimized alterations of the normal activation pattern if either the bifascicular representation or the diverging network is a valid representation of the left bundle branch. If the bundle is bifascicular, the incision would be placed about midway between the two fascicles in the peripheral ramification and should not significantly alter the normal activation pattern. If the bundle is a diverging network, the incision would be parallel to the general direction of the radially fanning fibers, resulting in minimal interruption of major centrifugal paths.

Some investigators have found P potentials several millimeters deep to the endocardial surface.[9,10] Others have disputed these findings.[11,12] In our preparations it is unlikely that cells deep to the first few layers survived in a nearly normal electrophysiologic state. If deep Purkinje fibers influence endocardial distribution by coursing in a direction parallel to the plane of the endocardium, their deterioration in this preparation would alter the normal activation pattern. We have not completely ruled out this possible source of error, which would have the effect of eliminating possible conduction pathways and prejudice the data in favor of the more parsimonious bifascicular representation. However, certain comparisons indicate that the preparation reproduces with little distortion the activation pattern existing in vivo. The interval from stimulus artifact to earliest M activa-

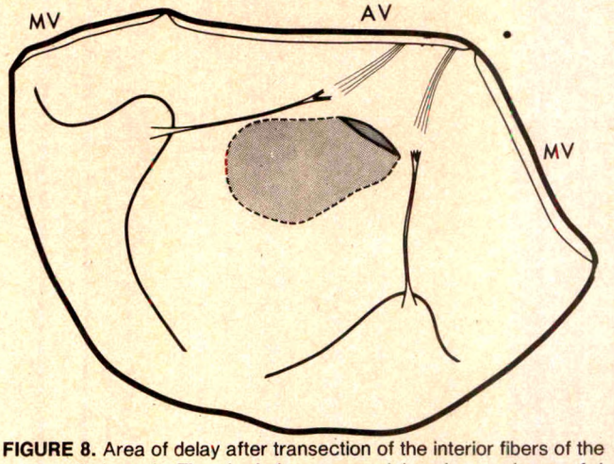

FIGURE 8. Area of delay after transection of the interior fibers of the left bundle branch. The shaded area was delayed a maximum of 4 msec. The incision was 8 mm long and interrupted 70 percent of the total width of the bundle at that level. See legend to Figure 4.

tion (15 to 25 msec, mean 21) is close to the interval from activation of the main left bundle branch to the earliest ventricular activation recorded in vivo.[13] The general pattern of M activation resembled the pattern observed in vivo in numerous studies[14–19]: (1) The earliest M activation occurred in the mid-septum; (2) the latest M activation occurred in the upper septum and tips of papillary muscles; (3) the papillary muscles were activated from base to apex. There is a discrepancy between our findings and those of one study performed in vivo. Venerose et al.[7] found that the total time required for P activation in the left ventricle of the intact heart was as great as 60 msec. In our preparations, the maximal time was 45 msec. This interval may be directly related to the size of the heart. We purposely used small or medium-sized hearts. The total time required for activation of M cells (30 to 50 msec) corresponds with the total time required for activation of the left ventricular subendocardial M cells in vivo according to some investigators,[16] although another group[14] found a somewhat shorter time.

Validity of representation of the left bundle branch as a bifascicular structure: The activation pattern of the left bundle branch network confirmed the visual impression that the interior network is a direct continuation of the proximal left bundle branch, not a derivation from the border fibers. The fibers in the interior network are activated nearly simultaneously with equidistant points on the borders. The isochronous lines of septal P activation showed few or no central indentations (proximal convexity). If these interior fibers were activated from the border fibers, as strict interpretation of the bifascicular representation implies, there should be relatively deep central indentations in the isochronous lines, resulting from the delay produced in transit from the border fibers to central points in the interior fibers. Uhley and Rivkin,[20,21] noting these interior fibers in stained specimens, represented the left bundle branch as a tripartite system composed of two "divisions" (border fibers) and the septal fibers. They observed subtle electrocardiographic changes resulting from incisions within the interior network. Myerburg et al[6] demonstrated this interior network by staining with iodine and recording P potentials from these fibers. They also showed nearly simultaneous activation of equidistant points in the interior and on the borders. However, they retained the terminology of the bifascicular representation, referring to the border fibers as "divisions." Our observations on the effects of lesions within the conduction system did not conform with the bifascicular representation. Transection of either group of border fibers (the "fascicles" or "divisions") did not produce delay in half of the endocardial surface. Delay occurred in parts of the paraseptal free wall and peripheral upper septum if the lesions extended substantially across the interior fibers. The area of delay was one third or less of the total endocardial surface (Fig. 8). The magnitude of delay (5 to 8 msec) was the same as that recorded by Myerburg et al.,[8] who produced similar lesions. However, in contrast to our findings they observed delay only in P cells, not M cells. This difference may be related to differences in the extent of the lesions. Most damaging to the bifascicular representation was the finding that interruption of both groups of border fibers ("bifascicular" block) did not produce complete block of conduction of the left bundle branch because of unincised interior fibers that originated in the main bundle branch.

Validity of representation of the left bundle branch as a fanning network: Representation of the left bundle branch as a fan-shaped network implies no functional distinction between border and interior fibers. Yet the border fibers have several distinctive characteristics. They pursue nearly straight paths for relatively long distances, as opposed to the more sinuous interior fibers (Fig. 1). Apparent conduction velocity is greater in the border fibers, particularly in the bridging strands, than in the interior network. The increase in the conduction velocity in the bridging strands is partly but not entirely due to their straight course. The more proximal border fibers, which are also straight, do not conduct as rapidly as the bridging strands, thereby indicating that there is a "real" as well as "apparent" increase in conduction velocity in the bridging strands. This may be due to a relative infrequency of lateral branches. Regardless of their significance with respect to cellular function, these apparent conduction velocities are significant since they measure the actual net rate at which impulses traverse the endocardial surface. Another distinctive feature of the border fibers is that the bridging strands crossing the cavity provide a shortcut to areas on the free walls. As a consequence of these anatomic and functional features, the border fibers are specialized for rapid transport to relatively distant sites on the free walls and papillary muscles. These differences between the serpentine interior fibers of the septum and the straight border fibers coursing to the free walls operate to synchronize activation of the free walls and septum despite the greater distance of the free wall from the main left bundle branch.

Incisional lesions and effect of transverse functional interconnections: These anatomic and functional differences between the border and interior fibers may be relevant to our observation that incisions that transected the border fibers resulted in greater delay over larger areas of the endocardial surface than incisions of comparable or greater size that interrupted the interior fibers. Interior incisions, which involved more than half of the width of the left bundle branch, produced delay of only a few milliseconds over only 10 or 15 percent of the left ventricular endocardial surface. This result indicates that functional transverse interconnections within the interior network provide activation from the unincised portions of the left bundle branch network to the fibers distal to the incision. This conclusion is also suggested by the visual appearance of the stained left bundle

branch network. Since transection of half of the left bundle branch from the border to the center did not result in delay over half of the endocardial surface, these functional interconnections must also provide some activation to the border fibers distal to the incision, thus serving to reduce the area of delay. However, there is no need to assume that the frequency or density of these interconnections is the same in the border fibers as in the interior network. Actually, by inspection the bridging strands usually have only a few lateral interconnections to the endocardial surface. Because the apparent conduction velocity in the interior is less than in the border fibers, and the wave front of activation lags slightly behind that in the border fibers, interconnections between interior fibers and border fibers would be less effective in overcoming delays produced by incisions of the border fibers. Moreover, interconnections with unincised fibers can supply activation from two directions into an area distal to an interior incision, but fibers distal to an incision of the border fibers can be supplied only from the one direction provided by interconnections with unincised interior fibers.

Clinical applications: The relevance of these data to man and clinical electrocardiography is uncertain since there are differences among species in the architecture of the His-Purkinje system.[3] It has been pointed out[4,21,22] that interruption of the border fibers of the left bundle branch of the dog results in axis shifts that are similar in direction but smaller in magnitude than those attributed in clinical electrocardiography to "fascicular block." However, some exponents of the bifascicular representation have attributed these differences in degree to the more vertical position of the canine heart[4] rather than to any essential difference in structure between the canine and human left bundle branch. It has been claimed[4] that if the canine heart is placed horizontally, axis shifts are more marked, like those in man. The left bundle branch of man has been grossly visualized by iodine staining only rarely; two reports[23,24] have shown illustrations from two normal human hearts. In both of these reports the left bundle branch is considered bifascicular and the illustrations are labeled accordingly, although neither illustration shows clear delineation of the two fascicles and interior fibers are apparent. Spach et al.[24] showed a stained canine left bundle branch with many interior fibers and commented on the similarity of the canine and human left bundle branches. Dissection of the left bundle branch is not a reliable means of elucidating its structure, since inconspicuous fibers may be overlooked. Histologic methods require examination of many contiguous samples in order to reconstruct the architecture of the left bundle branch. Two recent painstaking histologic studies[25,26] of the human left bundle branch reported an extensive interior network. These observations were interpreted as invalidating the bifascicular representation.

Our canine electrophysiologic data generally conform with these histologic observations. However, they do not exclude the possibility that certain implications of the bifascicular representation may be valid because of the distinctive features of the border fibers and the comparatively large areas that manifest delay after their interruption. It is acknowledged that shifts of the axis on the electrocardiogram may be associated with minimal or no prolongation of the QRS interval.[4] Therefore, we cannot discount the possibility that delay of activation of one third of the endocardial surface by 7 msec in the dog might result in a shift of the axis to the degree now termed "fascicular block." This question cannot be definitively resolved by our in vitro data.

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Electrophysiologic Antagonism of Quinidine and Bretylium Tosylate

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Interactions of quinidine (5 mg/liter) and bretylium tosylate (20 mg/liter) were studied in isolated perfused rabbit hearts by recording transmembrane potentials from the atrial fibers, the atrioventricular (A–V) junction and the ventricular fibers. The following observations were made on ventricular fibers. As expected, administration of quinidine prolonged action potential duration and reduced the maximal rate of depolarization. Subsequent addition of bretylium to quinidine shortened action potential duration and tended to restore the maximal rate of depolarization. The membrane resting potential, the action potential amplitude and overshoot showed no significant changes. With respect to A–V conduction, bretylium alone shortened intraatrial and His-Purkinje conduction times but prolonged intranodal conduction time. With quinidine, intraatrial and His-Purkinje conduction times were markedly prolonged and intranodal conduction time was only slightly increased. Addition of bretylium to quinidine shortened intraatrial and His-Purkinje conduction times but significantly prolonged intranodal conduction time, resulting in a further prolongation of the total A–V interval. The possible clinical implications of these findings are stressed.

Bretylium tosylate has been shown to be effective in the treatment of acute ventricular arrhythmias including ventricular fibrillation.[1–5] In addition to its postganglionic sympathetic blocking action, bretylium increases the ventricular fibrillation threshold and has a positive inotropic effect.[6,7] Reports differ on the electrophysiologic action of this agent on the myocardium.[8–10] Data from studies by Watanabe et al.[8] in rabbit ventricular fibers and those of Wit et al.[9] in canine Purkinje and ventricular fibers are quite contradictory (Table I). To clarify the electrophysiologic effects of bretylium, and to attempt to explain these discrepancies, we studied the interactions of quinidine and bretylium. Results of our previous studies[8,11] have indicated that these agents have contrasting electrophysiologic actions.

Methods

Experiments were performed in isolated perfused rabbit hearts using previously reported techniques[12] of isolation and perfusion. We used a modified Chenoweth's solution with the following composition in millimoles per liter: sodium chloride 119.8, potassium chloride 4.5, calcium chloride 2.4, magnesium chloride 2.1, sodium bicarbonate 25.0 and dextrose 10.0. The perfusion fluid was saturated with 95 percent oxygen plus 5 percent carbon dioxide.

A ventricular electrogram was recorded by two small surface electrodes attached to the right ventricular apex and the left ventricular base. A stimulating electrode was placed near the sinus node, and the hearts were driven at a constant rate 10 to 15 beats/min higher than the intrinsic sinus rate. Glass microelectrodes filled with 3 molar potassium chloride with tip resistances of 10 to 25 megohms were used to record transmembrane potentials from the atria, the atrioventricular (A–V) junction and the ventricular fibers. The potentials were amplified by a neutralized input capacity amplifier and Tektronix amplifiers. A Grass camera was used to photograph tracings on a Tektronix oscilloscope.

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TABLE I

Comparison of Membrane Effects of Bretylium on Ventricular Fibers

	Watanabe et al.[8] (1969)	Wit et al.[9] (1970)
Membrane resting potential	Increase	No change
Action potential amplitude	Increase	No change
Maximal rate of depolarization	Increase	No change
Action potential duration	Decrease	Increase
Effective refractory period	Decrease	Increase

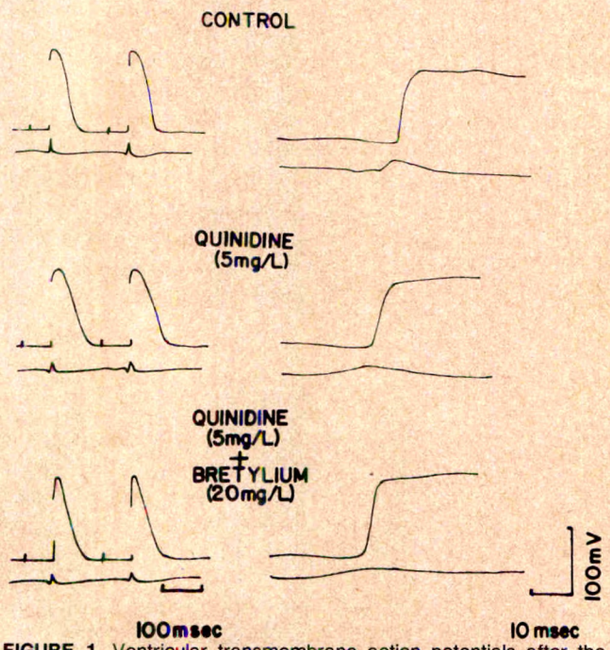


FIGURE 1. Ventricular transmembrane action potentials after the addition of quinidine and bretylium. **Column at right** shows high speed records of phase zero. After the addition of quinidine (5 mg/liter) there was an increase in action potential duration and a decrease in the maximal rate of depolarization. Subsequent addition of bretylium (20 mg/liter) restored the maximal rate of depolarization and reduced the action potential duration toward the control value.

The sequence of perfusion was as follows: (1) control (modified Chenoweth's solution), (2) control with quinidine (5 mg/liter), and (3) control with quinidine (5 mg/liter) and bretylium tosylate (20 mg/liter). Each perfusion lasted at least 30 minutes.

Results

Ventricular Fibers

Table II summarizes the effects of interaction of quinidine and bretylium on the action potential characteristics of ventricular fibers in 10 rabbit hearts. As expected, quinidine decreased the maximal rate of phase zero depolarization from 57.5 ± 14.6 (standard deviation) to 36.0 ± 8.9 v/sec and prolonged the action potential duration from 118.0 ± 22.0 to 147.0 ± 25.6 msec. Addition of bretylium to quinidine shortened the action potential duration to 135.0 ± 25.2 msec and restored the maximal rate of depolarization to 42.1 ± 12.1 v/sec. Thus, addition of bretylium reversed certain membrane effects of quinidine. These changes were statistically analyzed with use of the paired Student t test (Table II). The shortening of action potential duration was statistically significant, whereas the increase in maximal rate of depolarization was not. The membrane resting potential, the action potential amplitude and overshoot showed no changes.

Figure 1 shows the antagonism between quinidine and bretylium relative to the action potential contour of ventricular fibers in a typical experiment. Shortening of the action potential and an increase in the rate of phase zero depolarization after the addition of bretylium are evident.

A–V Conduction

In a secord series of experiments in another group of 10 rabbit hearts, A–V conduction was studied by recording transmembrane potentials from the A–V nodal fibers. Administration of bretylium alone had contrasting effects on different fiber types; action potential duration was prolonged in node-His (NH) fibers of the A–V node and shortened in ventricular fibers (Fig. 2). Figure 3 shows the effects of bretylium on conduction times in different portions of the A–V transmission system. Intraatrial (A) and His-Purkinje (HP) conduction times were shortened, but intranodal conduction time was prolonged. There was an increase in the total A–V interval.

TABLE II

Effects of Quinidine and Bretylium on the Ventricular Fibers of Rabbit Heart (means ± standard errors)

	APA (mv)	MRP (mv)	APD (msec)	MRD (v/sec)
Control	90.0 ± 9.1	64.8 ± 10.3	118.0 ± 22.0	57.5 ± 14.6
Quinidine alone	93.0 ± 11.3	69.4 ± 13.1	147.0 ± 25.6*	36.0 ± 8.9†
Quinidine and bretylium	92.8 ± 13.3	67.1 ± 9.6	135.0 ± 25.2†	42.1 ± 12.1

* $P<0.01$.

† $P<0.05$.

APA = action potential amplitude; APD = action potential duration; MRP = membrane resting potential; MRD = maximal rate of phase zero depolarization.

TABLE III

Combined Effects of Quinidine and Bretylium on A–V Conduction Time (means ± standard errors)

	Control (msec)	Quinidine (msec)	Quinidine and Bretylium (msec)
Atrial	25.6 ± 11.6	75.0 ± 6.6	63.6 ± 56.6
Nodal	43.8 ± 13.4	69.0 ± 37.5	100.2 ± 52.2†
His-Purkinje	30.2 ± 12.3	70.6 ± 24.7*	69.4 ± 28.8
A–V interval	99.6 ± 36.0	214.6 ± 102.8†	233.2 ± 105.4

* $P < 0.01$.
† $P < 0.05$.

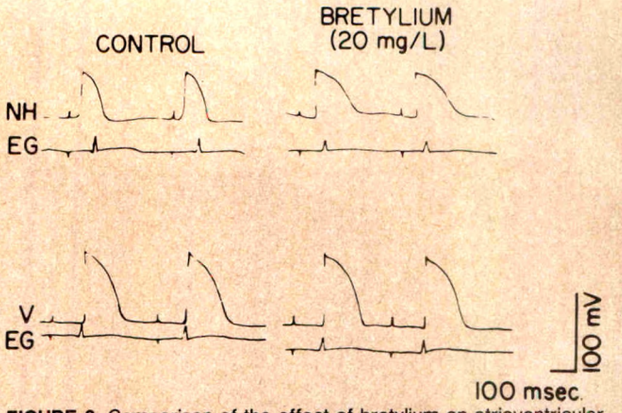
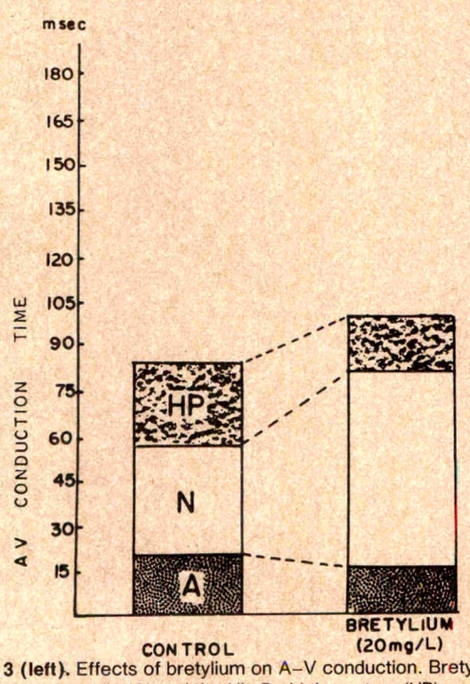


FIGURE 2. Comparison of the effect of bretylium on atrioventricular (A–V) nodal fibers (node-His region) and ventricular fibers. Action potential duration of the N–H fibers was prolonged but that of ventricular fibers was shortened. NH = node-His; EG = electrogram; V = ventricle.

The combined effects of quinidine and bretylium are shown in Figure 4. With quinidine, both intraatrial and His-Purkinje conduction times were markedly prolonged, and intranodal conduction was only slightly delayed. Subsequent addition of bretylium to quinidine shortened the intraatrial and His-Purkinje conduction times but significantly prolonged intranodal conduction time. However, the initial prolongation of the total A–V interval induced by quinidine was further exaggerated by the addition of bretylium. Table III shows the results of statistical analyses of these changes.

A–V nodal block produced by addition of bretylium to quinidine: Depression of intranodal conduction after the addition of bretylium to quinidine resulted in second degree A–V block in 5 of the 10 hearts. An example is shown in Figure 5. In this figure, transmembrane action potentials from an NH fiber and an electrogram are shown together with a ladder diagram. There was a 1:1 response to atrial stimulation in this proximal NH fiber, 3:2 conduction to the ventricles, and Wenckebach periodicity. The most interesting finding in this record is the sequential change in the NH action potentials. The first conducted atrial impulse is associated with a normal



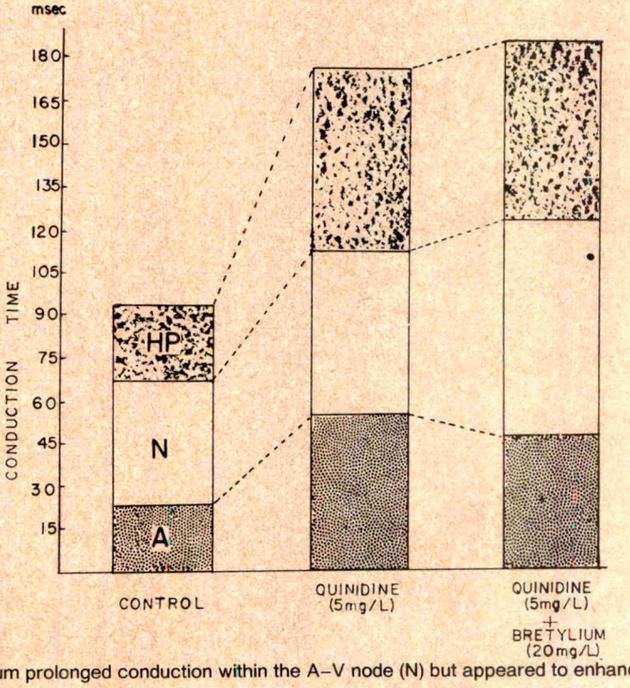


FIGURE 3 (left). Effects of bretylium on A–V conduction. Bretylium prolonged conduction within the A–V node (N) but appeared to enhance conduction within the atria (A) and the His-Purkinje system (HP).

FIGURE 4 (right). Quinidine (5 mg/liter) prolonged total A–V conduction time, with increases within the atria (A) and His-Purkinje (HP) regions. After the addition of bretylium, there was further prolongation of conduction time in the intranodal region (N) but some shortening within the atria and the His-Purkinje system. Hence, the addition of bretylium to quinidine may cause further A–V conduction delay.

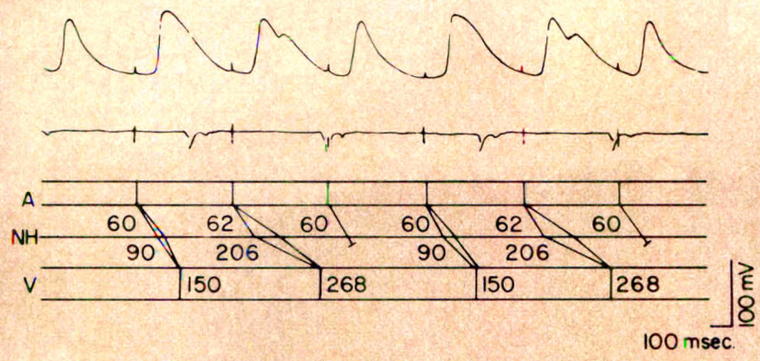


FIGURE 5. Wenckebach periodicity produced by bretylium in the presence of quinidine. The first conducted beat shows a rather normal-looking action potential in this proximal node-His fiber. The second beat shows decreased amplitude of the action potential followed by hump formation; finally, the third action potential is further diminished in amplitude and shows markedly shortened action potential duration. This beat is not conducted to the ventricles. Fragmentation of the wave front within the intranodal region is suspected, as indicated in the ladder diagram. A = atria; NH = node-His; V = ventricle.

action potential contour, but the second impulse produces an action potential with a reduced amplitude and upstroke velocity, showing a prominent hump formation in its repolarization phase. In this beat, conduction time is slightly prolonged between the sinus nodal region (stimulus artifact) and this fiber, and it is markedly prolonged below this layer of the A–V node. Finally, the third atrial impulse is associated with a still smaller and much narrower action potential, which fails to be propagated to the ventricles. The recordings in Figure 6, obtained 4 minutes after those in Figure 5, demonstrate that the site of block is most likely within the A–V node, and perhaps immediately below this fiber. This distal NH fiber shows a 3:2 response to atrial stimulation, again with progressive prolongation of the conduction time (Wenckebach phenomenon).

Discussion

Mechanism of Interaction of Bretylium and Quinidine

Several investigators[9,10,13] have indicated that the electrophysiologic action of bretylium tosylate differs from that of other antiarrhythmic agents such as quinidine. Wit and co-workers[9] and Bigger and Jaffe[10] reached this conclusion on the basis of their observations of initial enhancement of Purkinje fiber automaticity and the lack of significant effect on conduction velocity after bretylium was added to the perfusate. They reported that bretylium, like quinidine, prolongs action potential duration. In sharp contrast, Watanabe et al.[8] have shown a shortening of the ventricular action potential and an increase in conduction velocity after administration of bretylium. This discrepancy prompted us to study the interaction of quinidine and bretylium. We found that bretylium shortened the action potential duration initially prolonged by quinidine (Table II, Fig. 1). Bretylium also tended to restore the maximal rate of phase zero depolarization, which had been reduced by quinidine, although the change was statistically not significant. These results appear to reconfirm our previous observations.[8] They are in contrast with the results of Wit et al.[9] and Bigger and Jaffe,[10] who reported a prolongation of the action potential duration and the refractory period by bretylium.

In a previous study,[8] we showed by means of a tissue bath that bretylium increased the membrane resting potential, the action potential amplitude and the maximal rate of depolarization of ventricular fibers, although Wit et al.[9] and Bigger and Jaffe[10] observed no significant changes in these variables. However, Bigger and Jaffe reported an increase in membrane resting potential in fibers with an initial resting potential of lower than normal value. Similarly, Wit et al.[9] noted occasional hyperpolarization induced by bretylium, especially when the membrane resting potential was reduced or the tissue was considered hypoxic. They explained such findings by possible release of catecholamines from the sympathetic nerve endings. Although these points will be discussed in greater detail elsewhere (Watanabe et al., in preparation), it is conceivable that this mechanism played a role in the hyperpolarization and increased conduction velocity observed in our previous experiments.[8] It is unlikely that the same mechanism

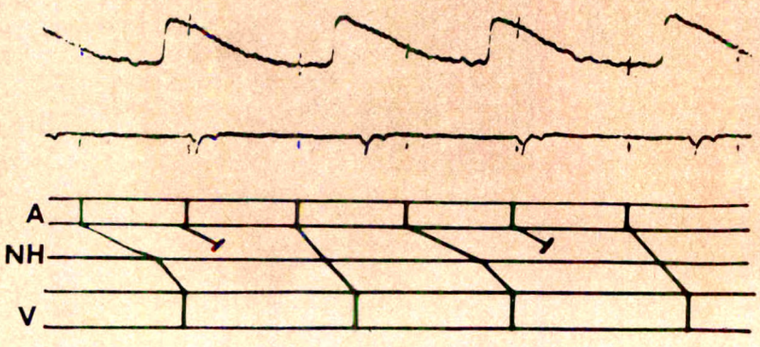


FIGURE 6. Wenckebach periodicity after administration of quinidine and bretylium, with 3:2 conduction and block above the distal node-His fiber. The ladder diagram shows the sequence of conduction. Abbreviations as in Figure 5.

prevailed in the present study of isolated hearts perfused through the coronary system since myocardial oxygenation in this setting should be better than in a tissue bath experiment and recirculation of released catecholamines could not play a major role. Absence of this mechanism may explain why the addition of bretylium to quinidine did not change the membrane resting potential or the action potential amplitude and overshoot in the present study (Table II).

All the effects of bretylium cannot be attributed to catecholamine release since this agent shortened the action potential duration both alone in the tissue bath experiments and in the perfused heart in the presence of quinidine. Furthermore, if catecholamine release were solely responsible for the electrophysiologic action of bretylium, one would not expect significant depression of intranodal conduction by this agent, whether used alone or after perfusion with quinidine. Cervoni et al.[14] showed that bretylium increased fibrillation threshold in both reserpine-pretreated and chronically sympathectomized dog hearts and concluded that the antiarrhythmic effects of bretylium are due to a direct action on the myocardium rather than to its adrenergic blocking action or its ability to release norepinephrine. In their study the positive inotropic effect of bretylium was apparently not dependent on catecholamine release since it was demonstrated after sympathectomy[6] and in reserpinized dogs.[7]

We have previously pointed out that extracellular potassium concentration significantly modifies the membrane effects of various antiarrhythmic agents[11,15] as well as the effects of electrolytes such as magnesium.[16] Since Bigger and Jaffe[10] used Tyrode solution with a much lower potassium concentration (2.7 millimoles) than that of ours (4.5 millimoles), the difference between their results and ours may be explained on this basis. However, since Wit et al.[9] used a concentration (4.0 millimoles) similar to that of our study, the discrepancy between their results and ours remains unexplained by this hypothesis. One might argue that bretylium tends to correct disturbances in membrane permeability and ion flux caused by either anoxia or quinidine medication, thereby restoring normal membrane resting potential and action potential characteristics, but has no or little effect on these variables in the absence of such disturbances. However, this hypothesis is speculative and does not explain the depression of intranodal conduction induced by bretylium. Another possible explanation for the discrepancy in results is the difference in species used. Both Wit et al.[9] and Bigger and Jaffe[10] studied canine hearts whereas we used rabbit hearts. Thus it may be of interest to study the interaction of quinidine and bretylium in canine preparations.

Clinical Implications

Antagonistic effects of bretylium and quinidine: Our present study clearly indicates antagonistic effects of bretylium and quinidine on the duration of action potential and the refractory period in ventricular fibers. Earlier, Bacaner[2] had indicated that the ideal effects of bretylium might not be achieved in the presence of quinidine-like agents. Similarly, Bernstein and Koch-Weser[17] have shown that other antiarrhythmic agents antagonized the clinical efficacy of bretylium when given concurrently or in direct proportion to their duration of use preceding administration of bretylium. Our present results confirm these clinical observations and suggest the following implications.

Bretylium tosylate usually is not chosen as the initial antiarrhythmic drug, but is resorted to when other antiarrhythmic agents have failed to control certain rhythm disorders. Since its electrophysiologic action differs distinctly from that of other agents, it may be able to terminate pathophysiologic mechanisms of arrhythmia that do not respond to other drugs. On the other hand, if bretylium is administered immediately after a quinidine-like agent, it may fail to control the arrhythmia because of antagonism between the drugs. Hence, it may be necessary to withdraw antiarrhythmic agents to utilize the favorable effects of bretylium.

Additive effects of bretylium and quinidine on A–V conduction: Finally, it must be stressed that quinidine and bretylium have contrasting effects on A–V conduction. Indeed, bretylium tended to shorten the intraatrial and His-Purkinje conduction times initially prolonged by quinidine (Table III) although it markedly depressed intranodal conduction, either alone or in the presence of quinidine. As a result, the total A–V interval was prolonged and second degree A–V block developed in some instances. Thus, the combination of quinidine and bretylium may have additive effects on A–V transmission, depressing conduction in all three portions of the A–V conducting system. Some clinical data appear to be at variance with these experimental results. Bacaner[18] (quoting Sanna et al. and adding his own case) reported improved A–V conduction in patients with second degree or higher grades of A–V block. In two cases (Fig. 10 and 11 of Bacaner),[18] the block was associated with narrow QRS complexes and Wenckebach phenomenon. This combination usually indicates an intranodal conduction disturbance,[19,20] but in some instances may be caused by block within the His bundle rather than within the A–V node.[21] Furthermore, Figure 5 of Bacaner's paper[18] (again reproduced from Sanna et al.) clearly indicates that the bretylium-induced improvement of A–V conduction occurred in the presence of A–V block with wide QRS complexes and that bretylium also shortened the QRS duration. Thus, normalization of His-Purkinje rather than intranodal conduction cannot be ruled out in those patients.

Other factors may also be involved in clinical cases. Dhurandher et al.[22] described a patient (their Case 1) who had second degree A–V block during treatment with bretylium, but attributed the block to posterior wall infarction rather than to the effects of the drug. Hence, although production of second degree A–V block by bretylium may be a rare event in the clinical setting, this possibility should be kept in mind, particularly in patients who already have some degree of A–V conduction disturbance.

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Effects of Intraperitoneal Administration of Propranolol on the Mouse Heart

Histochemical and Electron Microscopic Observations

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In an earlier investigation, ultrastructural and histochemical abnormalities were reported in the hearts of mice receiving the beta adrenergic blocking agent propranolol. Because of the increasing use of this drug to treat human cardiac disorders, we repeated this investigation. Our findings do not confirm that cardiac lesions are produced by propranolol: No structural or histochemical abnormalities could be related to administration of the drug. We conclude that there is no presently acceptable histologic evidence that propranolol causes myocardial damage.

Because propranolol is widely used to treat patients with heart disease,[1] it is of considerable importance that Sun et al.[2] have reported histochemical and electron microscopic changes in mice receiving this drug. In this investigation we repeated their study.

Material and Methods

The study was performed in three parts referred to as experiments 1, 2 and 3. The animals were 3 week old Swiss white mice averaging 20 g in weight. Propranolol (Inderal®, Ayerst Laboratories) was injected intraperitoneally once daily for 21 days in test animals; all control mice received daily injections of a similar quantity of sterile diluent. On the 22nd day the animals were killed by cervical traction, the thoracic cavity was swiftly exposed and the hearts were promptly treated as described later. Specimens were given code numbers and initial microscopic observations were made without knowledge of the experimental regimen to which they had been subjected. The code was then broken and the sections were reexamined.

In experiment 1, five mice received 0.05 mg of propranolol daily, five received 0.1 mg of the drug and five served as control animals. All hearts were fixed with glutaraldehyde, portions were removed for electron microscopic studies, then the remaining tissue was embedded in paraffin, sectioned and stained with hematoxylin-eosin.

In experiment 2, ten mice were given 0.1 mg of propranolol daily, and five received sham injections for control studies. The hearts of four treated and two control animals were perfused for electron microscopic studies. The remaining nine hearts were frozen for histochemical processing.

In experiment 3, fourteen mice received 0.1 mg of propranolol daily and another 16 mice served as control animals. Both groups gained weight at a similar rate. Three hearts from each group were perfused for electron microscopic studies and three others from each group were frozen for histochemical examination. The remaining 18 hearts were fixed in Bouin's solution, and 2 mm thick transverse slices of the ventricular region were embedded in paraffin, then sectioned for periodic acid-Schiff and hematoxylin-eosin staining. To insure uniform treatment, one experimental and one control specimen were embedded side by side in each paraffin block and processed together.

For electron microscopic studies, 3.5 percent glutaraldehyde in 0.1 molar cacodylate buffer was injected into the left ventricle of the beating heart through a 27 gauge needle. The heart was arrested and removed and the atria plus portions of the ventricles and interventricular septum were immersed in the glutaraldehyde solution for 3 hours, washed overnight in cacodylate buffer, then postfixed for 2 hours in 1 percent osmium tetroxide. After dehydra-

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Manuscript accepted October 4, 1973.

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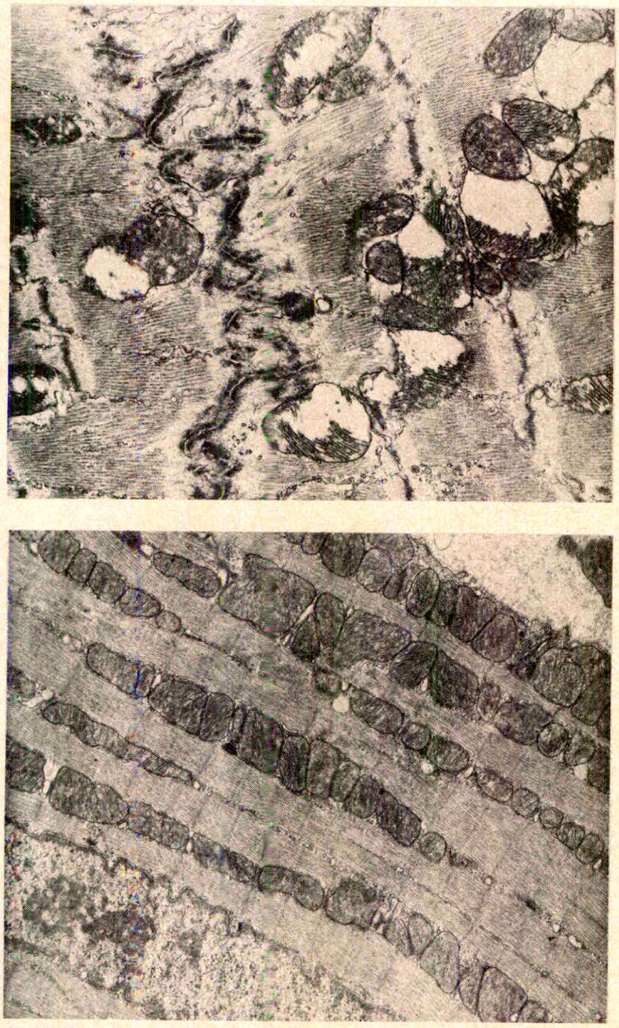

FIGURE 1. Electron micrographs of left ventricular tissue of mice from experiment 3. **Top,** control heart. Many mitochondria are swollen and have disrupted cristae. **Bottom,** treated heart (0.1 mg of propranolol). No ultrastructural abnormalities are present. **Top,** × 13,500; **bottom,** × 10,000, both reduced by 28 percent.

tion, tissue blocks were embedded in an Epon-Araldite plastic mixture.[3] Thin sections were stained in 25 percent uranyl acetate[4] and lead citrate[5] and examined in a Hitachi HU II-B electron microscope. Multiple samples, both adluminal and deeper, were examined from every heart, with several from each atrium, each ventricle and the interventricular septum.

For histochemical processing, hearts of simultaneously killed mice were swiftly excised without pinching or other mechanical injury, assembled in uniform orientation on a copper planchette and frozen in liquid nitrogen or isopentane slurry. Each planchette held one control and one or two treated hearts. Ten μ coronal sections were cut in a cryostat microtome, with at least six whole heart sections including all chambers for each of the following techniques: (1) Sudan black B for lipids[6]; (2) periodic acid-Schiff for glycogen, with diastase controls[6] (fixation by formaldehyde fumes and Carnoy's solution); and (3) enzyme activity determinations: succinic dehydrogenase,[6] nicotinamide-adenine dinucleotide, reduced form (NADH) diaphorase,[6] beta-hydroxybutyric dehydrogenase,[6] 5′-nucleotidase[7] and myofibrillar (calcium-activated) adenosine triphosphatase.[8]

Results

Electron microscopy: No consistent differences were observed between sections from tissues of propranolol-treated and control mice. Although ultrastructural anomalies were sometimes noted, they occurred with equal frequency in the control and treated groups. Occasionally, isolated mitochondria were swollen and cristae were disrupted or absent (Fig. 1, top). Less commonly there was a separation of myofibrils at the region of the intercalated disc. There was considerable variation in the amount of glycogen granules among sections but no difference between propranolol-treated and control groups. The great majority of sections of treated hearts appeared entirely normal (Fig. 1, bottom).

Histochemistry: Experimental animals could not be differentiated from control animals after repeated careful scrutiny. Total glycogen content varied from heart to heart but not in any systematic way. There were occasional features that might be taken as abnormal but they were no more frequent or marked in experimental than in control animals (Fig. 2). Most were probably artifacts, which are unavoidable in histochemical studies. Reduced oxidative enzyme activity was often evident in the region of intercalated discs in all hearts. No differences in blood vessel caliber or staining were evident. No pronounced 5′-nucleotidase activity was observed in myofibers of any of the hearts. Overall enzyme activity levels were similar in control and treated hearts.

Discussion

In our study, in contrast to that of Sun et al.,[2] it was not possible to distinguish the hearts of control and propranolol-treated mice on the basis of ultrastructural or histochemical characteristics. Although we observed occasional features resembling those interpreted as lesions in the earlier study, they were neither more abundant nor more conspicuous in treated than in control animals. We interpret these features as artifactual or, in some instances, normal.

If this interpretation also holds for the "lesions" of Sun et al., as seems probable, then an explanation must be sought for the reported association with administration of propranolol. Systematic artifacts could result if the control and experimental tissues were handled differently although the reported correlation between the dose of propranolol and the degree of abnormality is difficult to explain on this basis.

Alternatively, the drug may have produced true lesions that were overlooked or failed to appear in our study. Since only small samples of tissue can be inspected at sufficient magnification for ultrastructural resolution in the electron microscopic studies, sporadic abnormalities might escape detection, but it is unlikely that frequent or extensive lesions were missed. As for the possibility that true lesions appeared in the earlier study but not in our investigation, various agencies could be responsible. Mice of different age or strain might be differently affected

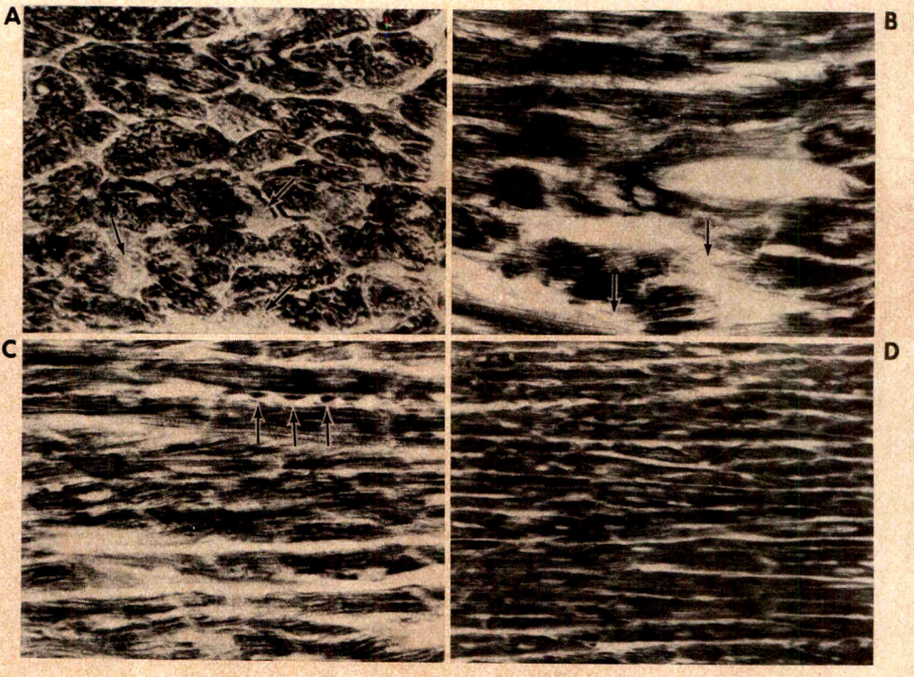

FIGURE 2. Histochemical pseudolesions. All sections are from the left ventricle, and all except one **(A)** are stained for succinic dehydrogenase activity. **A,** control heart: NADH diaphorase activity. Cross section showing areas of low intensity **(arrows)** resembling the "loss of mitochondria" in Figure 1 of Sun et al.[2] **B,** control heart: longitudinal section with discontinuity of fibers **(arrows)** similar to the "fragmentation" in Figure 3 of Sun et al.[2] This is actually a plane-of-section effect. **C,** control heart: longitudinal section showing areas of high intensity **(arrows)** resembling the "clumping of the mitochondria" in Figure 3 of Sun et al.[2] **D,** treated heart (0.1 mg propranolol): representative longitudinal section lacking evident abnormality. **A** to **C** × 600, **D** × 280, all reduced by 38 percent.

by the drug, but in both studies the animals were of the same strain and of similar initial weight. Some aspect of the environment, health or handling of the mice might conceivably have resulted in enhanced susceptibility to the drug in the earlier study. Sun et al. did not state whether their control mice were sham-injected as ours were. If not, differential stress might have been a factor. A difference in the potency or purity of the drug is unlikely since the source was the same. Similarly, the route of administration and largest dose used were alike in both studies. Sun et al. did not indicate how long after the last injection their mice were killed. This might be a significant variable.

In the earlier study the histochemical results were apparently dissimilar for different mitochondrial enzymes. Marked lesions were found for succinic dehydrogenase and "lactic dehydrogenase" (the technique primarily reveals NADH diaphorase activity), yet the authors reported "relatively little change in cytochrome oxidase and alpha-glycerophosphate dehydrogenase activity" and only a "generally increased" activity of beta-hydroxybutyric dehydrogenase. One would expect all mitochondrial enzymes to be affected in areas of mitochondrial abnormality. Virtually identical results were obtained in our study for the three oxidative enzymes examined (succinic dehydrogenase, NADH diaphorase and beta-hydroxybutyric dehydrogenase).

To minimize the risk of interpretive bias, our initial observations were made without foreknowledge of the treatment history of the specimens.

To minimize fixation artifacts in the electron microscopic aspect of the study, we perfused the hearts with glutaraldehyde. Sun et al. excised multiple samples and fixed these by immersion in osmium tetroxide. The delay involved in such a procedure is undesirable in a metabolically active, aerobic tissue. Also, Sun et al. froze for histochemical processing heart tissue remaining after excision of samples for electron microscopic studies, with both delay and mechanical trauma. Although artifacts can never entirely be eliminated, we consider our procedures less likely to produce them.

Clinical implications: Although a negative proposition cannot be proved, our results do not support the contention that propranolol in the doses used produces electron microscopic, histochemical or other histologic evidence of cardiotoxicity in mice. This is reassuring in view of the widespread utilization of propanolol in treatment of cardiac arrhythmias,[9] angina pectoris[10] and hypertension.[11] As recommended by Sun et al.,[2] careful observation must be continued in human subjects receiving propranolol. Clinical surveillance is justified because of the known side effects of this drug, but our study provides no evidence of myocardial damage.

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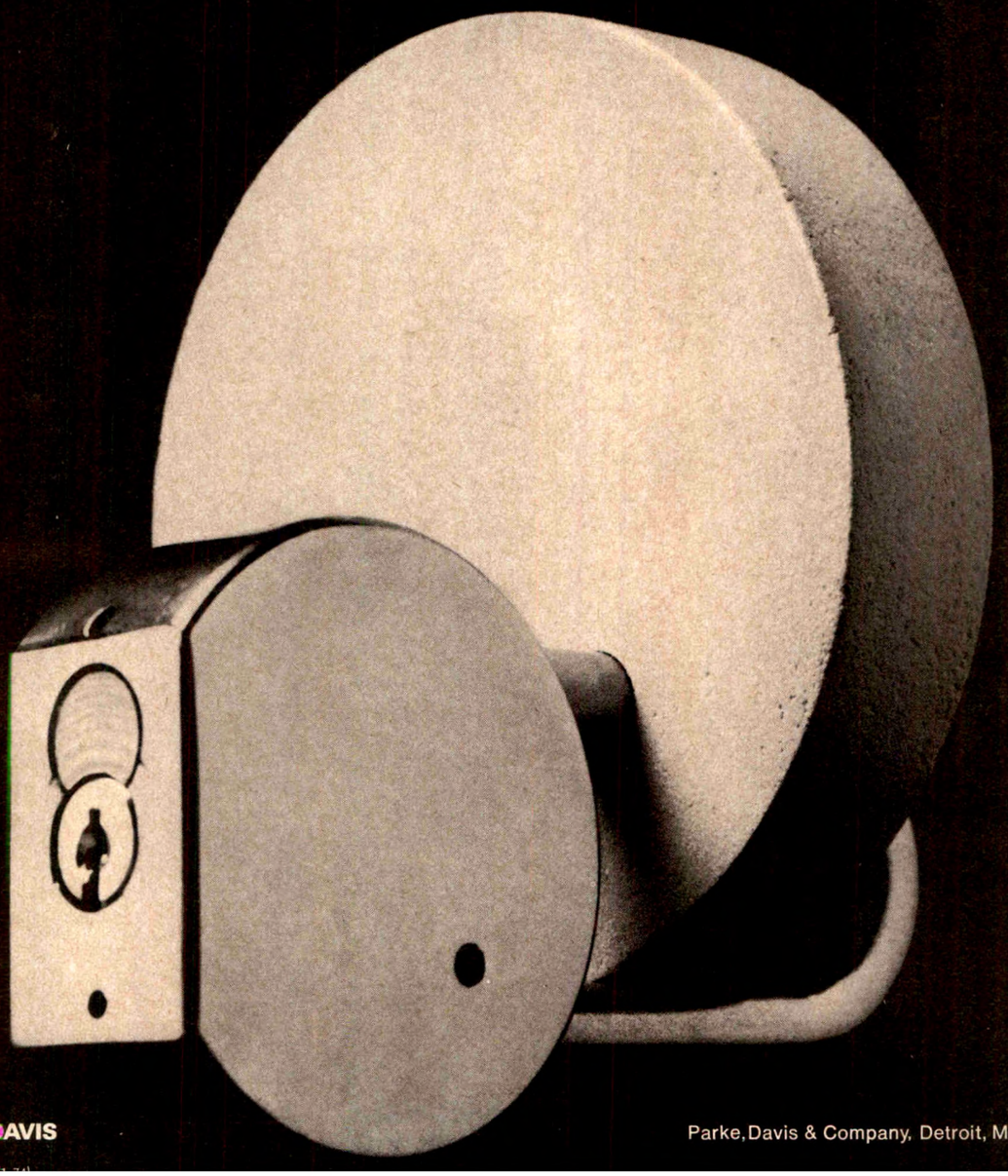

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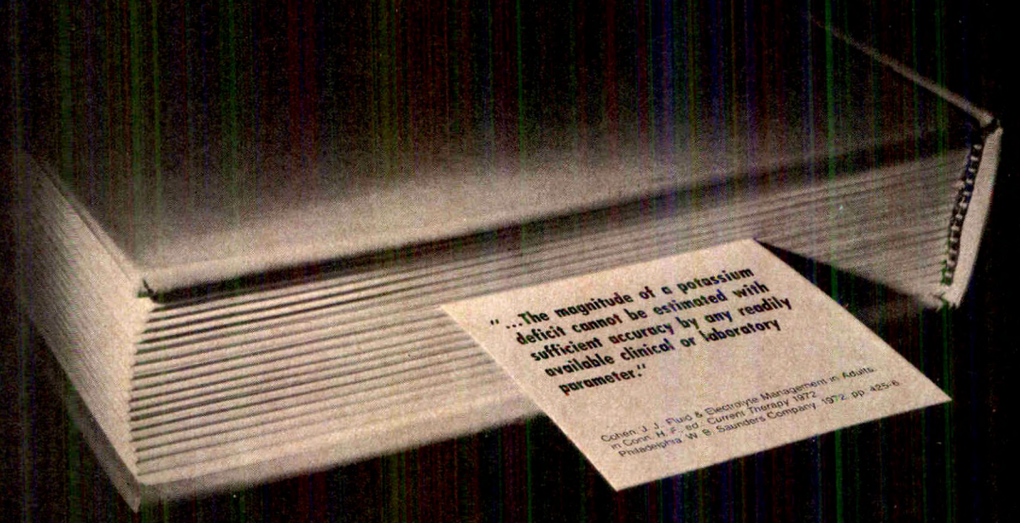

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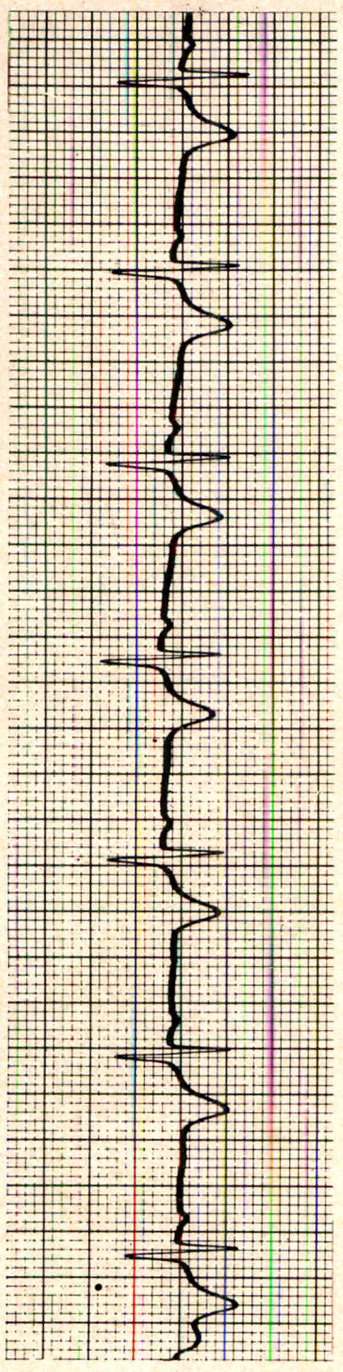

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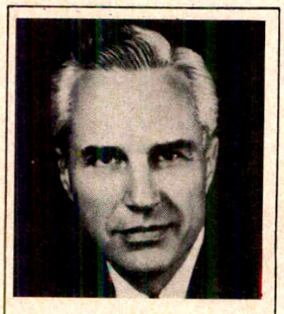

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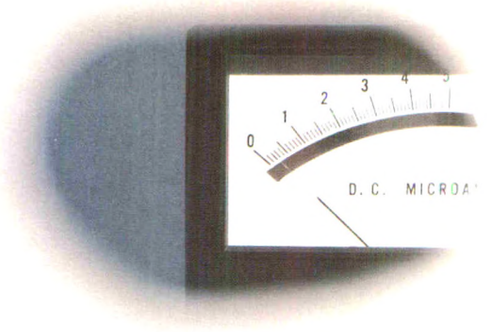

When defibrillating or using an electrocautery, the Bentley Trantec Transducer is safe without disconnection from the monitoring equipment. The high insulation materials used provide protection of both the device and the patient. This major advantage allows continuous monitoring of the patient during the critical time when these procedures are necessary.

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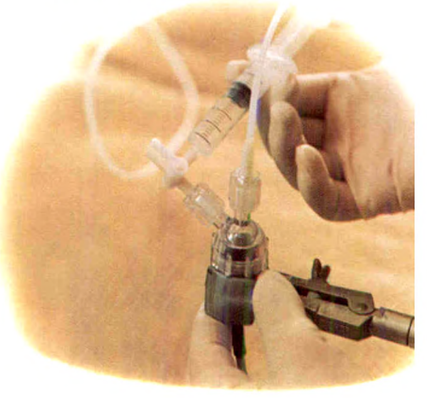

All Bentley Trantec Pressure Transducers are manufactured and tested to rigid specifications. Provided with a spare lexan dome which has two male linden fittings which allows connection to any standard catheter or blood connection fitting.

The clear lexan dome allows visual bubble detection and ease of elimination.

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Arterial

Pressure Range	0 to 300 mm of mercury
Overload Rating	6,000 mm of mercury
Excitation	10 volts maximum, DC or RMS carrier
Sensitivity	50 microvolts per volt per cm of mercury (±1%)
Volume Displacement	0.04 cu mm per 100 mm of mercury
Size	2.5 cm diameter by 3.6 cm long, exclusive of fittings
Weight	20 grams, exclusive of cable
Nominal Bridge Resistance	400 ohms
Pressure Connection	2 male linden fittings
Electrical Connection	Connector to operate with customer specified monitor
Non-Linearity & Hysteresis	1% of full scale, maximum
Leakage Current	Less than 0.2 micro-ampere RMS maximum, at 118 volts RMS AC, 60 Hz
Insulation	Withstands 10,000 volts DC
Sterilization Capability	Ethylene oxide gas, liquid disinfectants or emergency steam autoclave
WARRANTY	UNCONDITIONALLY GUARANTEED FOR ONE YEAR

Venous

Pressure Range	−10 to 60 mm of mercury
Overload Rating	3,000 mm of mercury
Excitation	10 volts maximum, DC or RMS carrier
Sensitivity	250 microvolts per volt per cm of mercury (±1%)
Volume Displacement	0.4 cu mm per 100 mm of mercury
Size	2.5 cm diameter by 3.6 cm long, exclusive of fittings
Weight	20 grams, exclusive of cable
Nominal Bridge Resistance	400 ohms
Pressure Connection	2 male linden fittings
Electrical Connection	Connector to operate with customer specified monitor
Non-Linearity & Hysteresis	1% of full scale, maximum
Leakage Current	Less than 0.2 micro-ampere RMS maximum, at 118 volts RMS AC, 60 Hz
Insulation	Withstands 10,000 volts DC
Sterilization Capability	Ethylene oxide gas, liquid disinfectants or emergency steam autoclave
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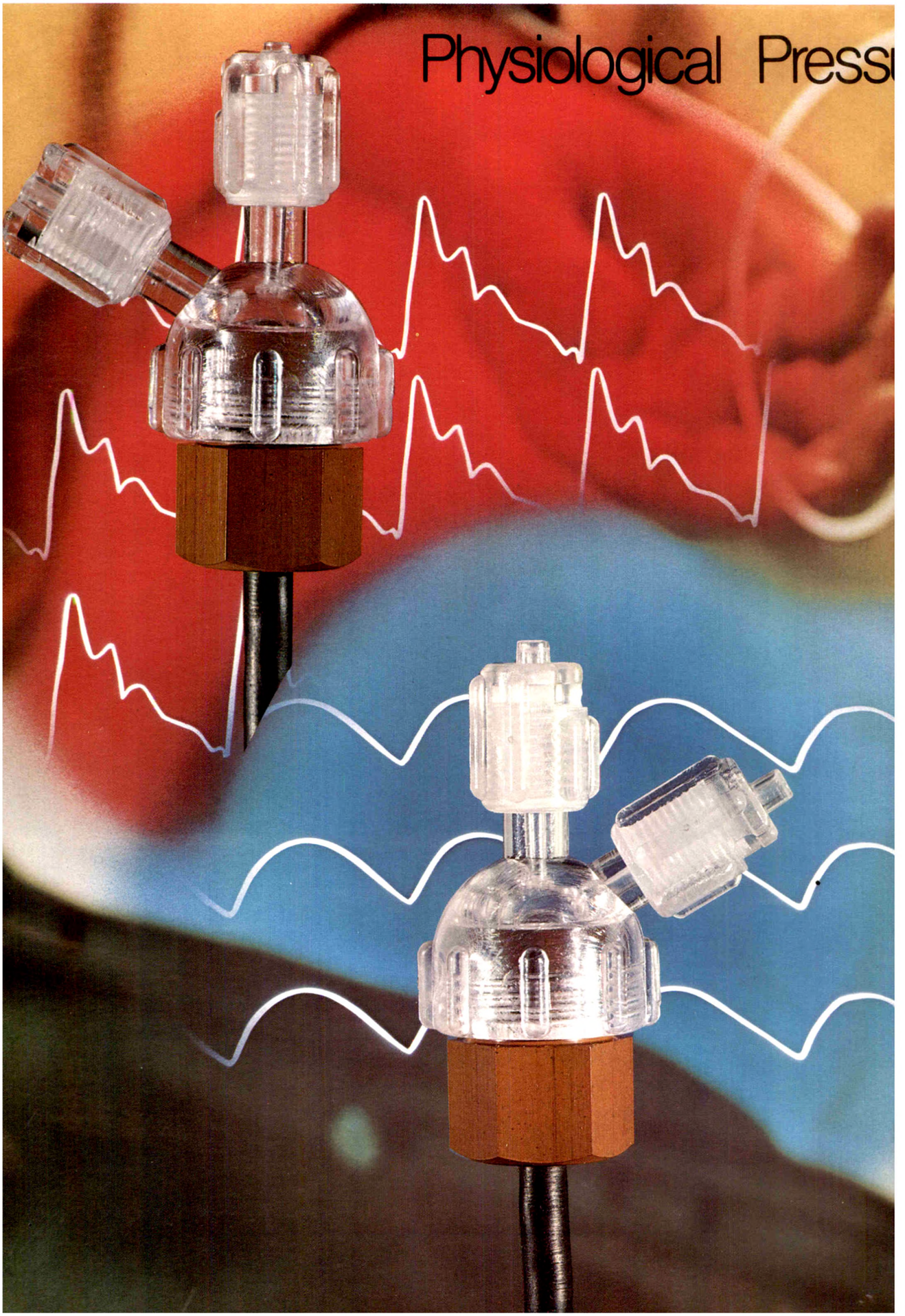
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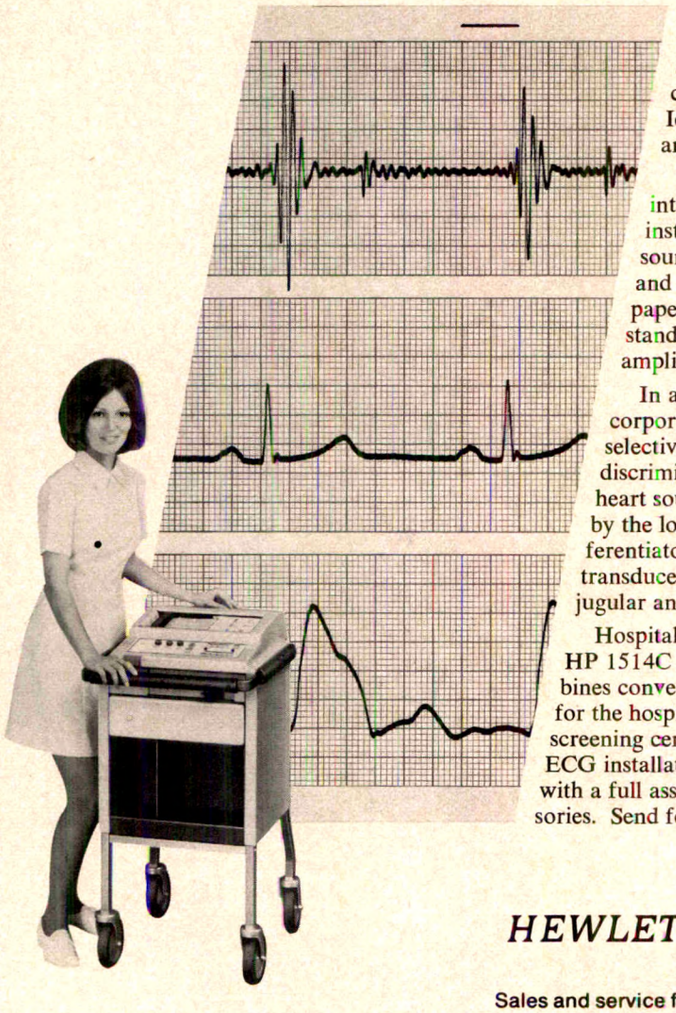

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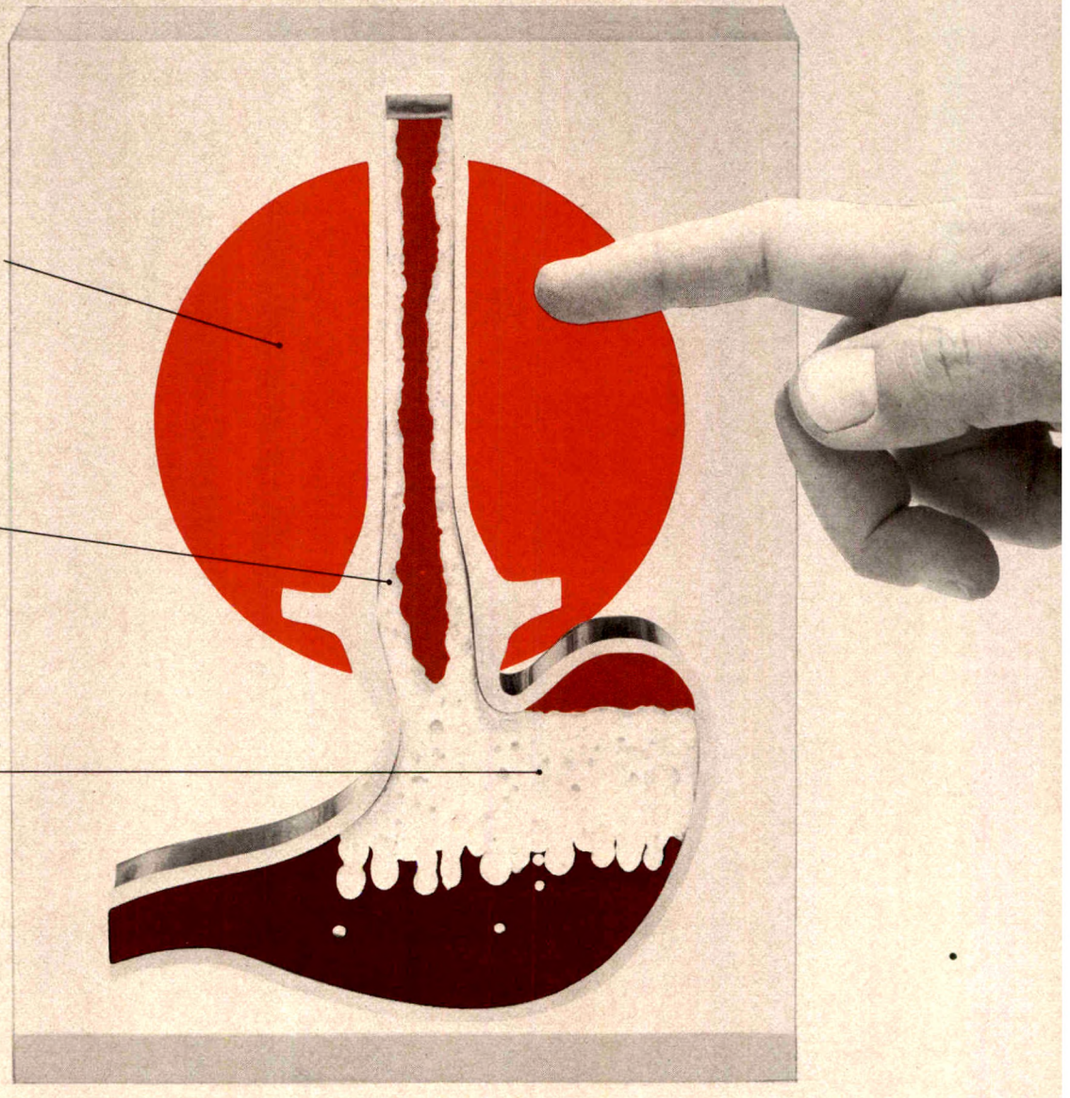

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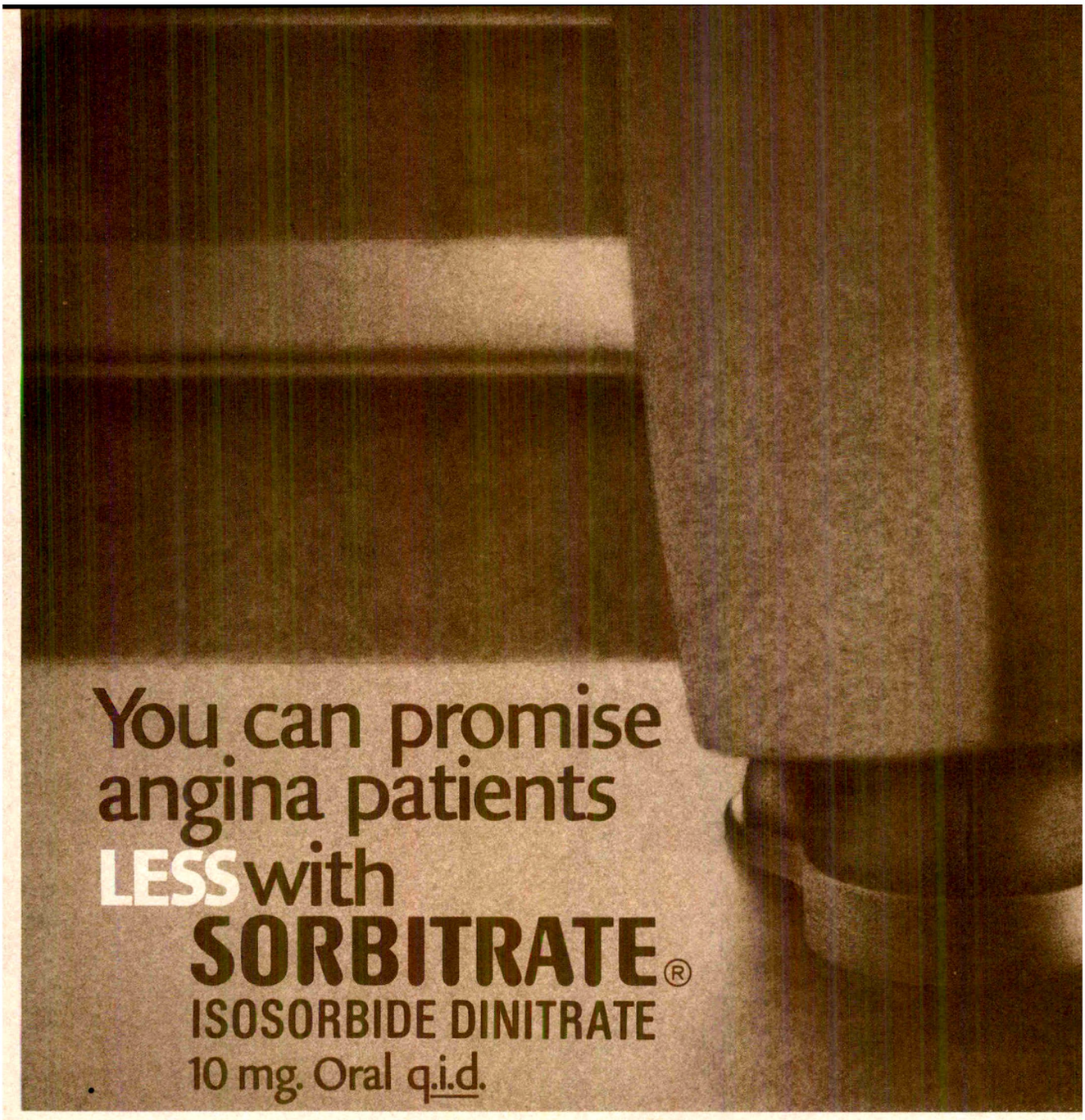

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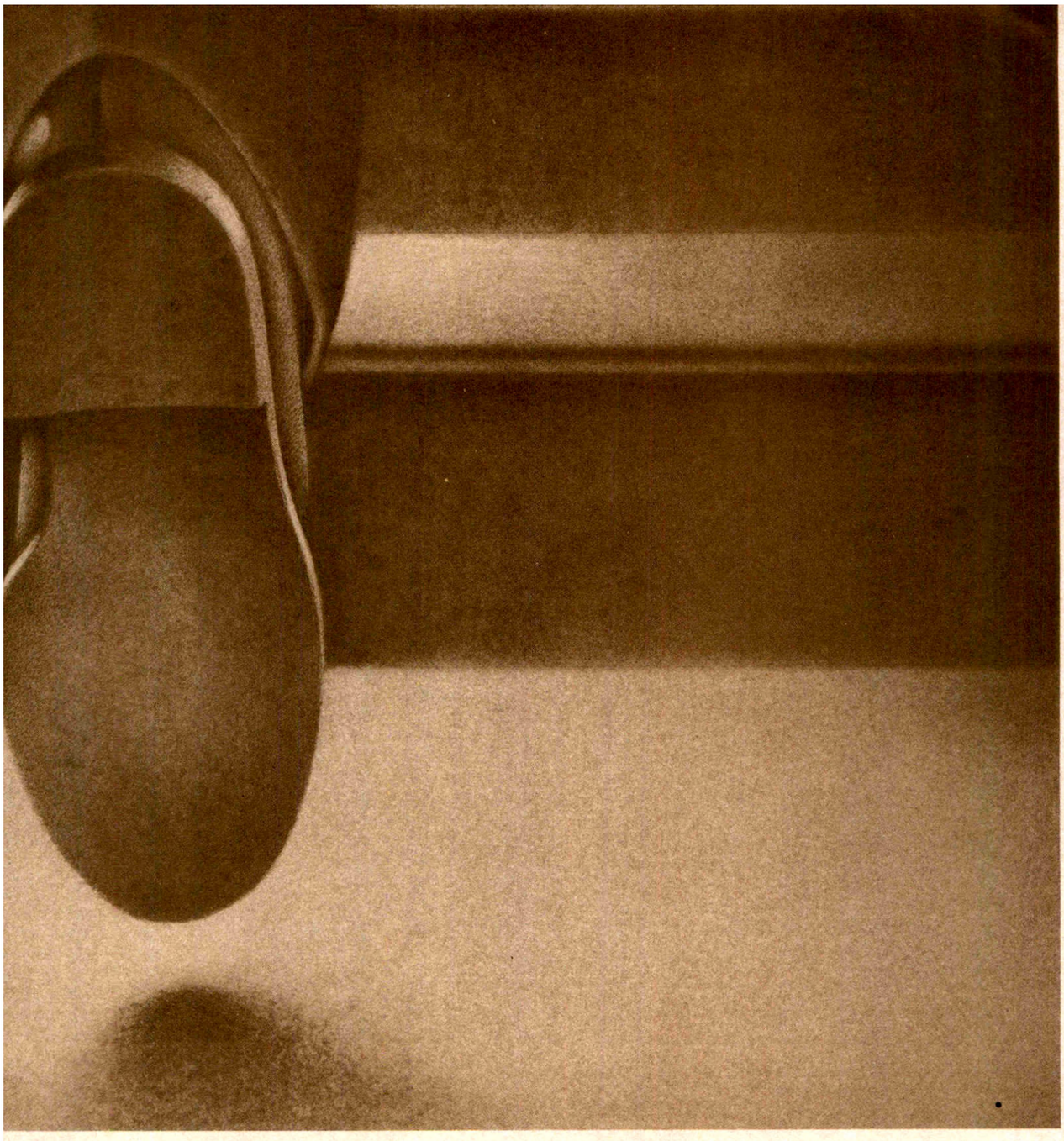

MARY OF PRESCRIBING INFORMATION

lications: Based on a review of this drug by the National Academy Sciences—National Research Council and/or other information, A has classified the indication as follows:
"Possibly" effective: For the treatment of angina pectoris.
Final classification of the less-than-effective indications require ther investigation.

raindications: A history of sensitivity to the drug.
nings: Data supporting the use of nitrates during the early days of acute phase of myocardial infarction are insufficient to establish y.
autions: Should be used with caution in patients who have glaucoma. ance and crosstolerance to other nitrates may occur.
erse Reactions: Headache which may be severe and persistent. ering the dose and using analgesics will help control the headaches h usually diminish or disappear as therapy is continued.
dverse reactions seen occasionally: Cutaneous vasodilation with ning; transient dizziness and weakness as well as other signs of bral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Oral tablets.

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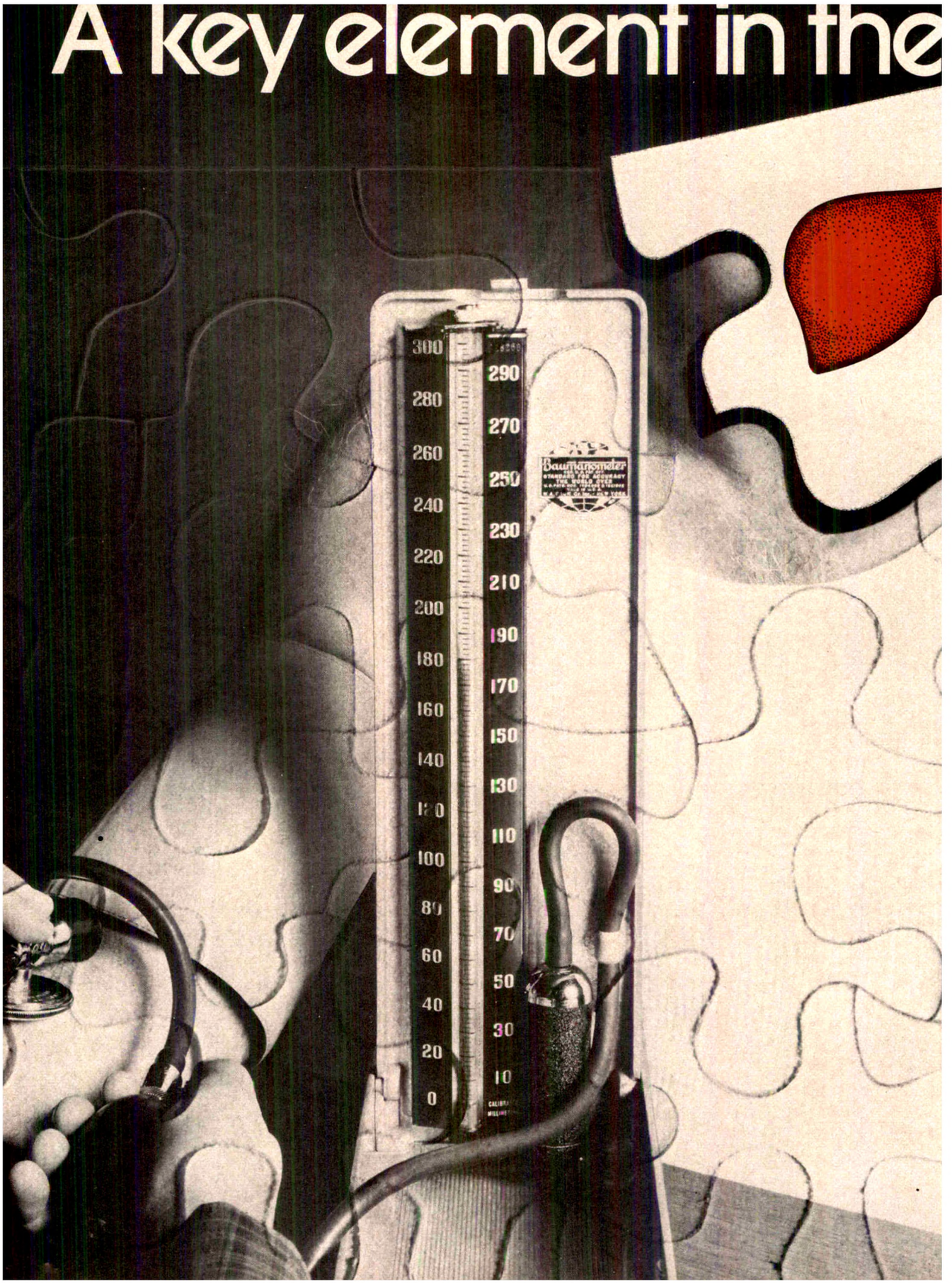
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hypertension puzzle

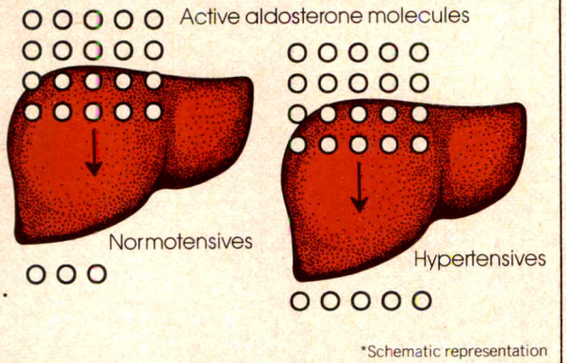
The liver metabolizes significantly less aldosterone in hypertensives than in normotensives.[1,2]

A significantly decreased hepatic MCR (metabolic clearance rate) of aldosterone, without significantly decreased SR (secretion rate), was demonstrated in approximately 90 percent of a group of 56 patients with benign essential hypertension.[1]

Thus "Failure of the aldosterone SR to fully adapt to the decrease in MCR may be responsible for a relative state of hyperaldosteronism in many patients with BEH [benign essential hypertension], even when the secretion and excretion rates are within normal range.

"It is conceivable that it is the mineralocorticoid [aldosterone] excess that is leading to an increase of sodium content in the arteriolar wall and the hypertensive process itself, in many patients with BEH."[2]

Metabolic clearance of aldosterone in hypertensives and in normotensives*



*Schematic representation

To help control the aldosterone factor in essential hypertension

Aldactazide®

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- Spironolactone blocks the pressor effect of aldosterone at the arteriole,[3-5] and exerts natriuretic action in the distal renal tubule.
- Hydrochlorothiazide exerts additive antihypertensive effect through its action at a different renal site.
- Aldactazide helps maintain potassium balance—without the need for potassium supplements—because the potassium-sparing action of spironolactone offsets the potassium-losing effect of hydrochlorothiazide.

References: 1. Genest, J., in Thorn, G. W., and Melby, J. C. (Editors): Aldosterone in Clinical Medicine, Medcom® Learning Systems, New York, Medical Communications, Inc., 1972, pp. 64-75.
2. Nowaczynski, W.; Kuchel, O., and Genest, J., in Genest, J., and Koiw, E. (Editors): Hypertension '72, Berlin, Springer-Verlag, 1972, pp. 244-255.
3. Crabbé, J.: Acta Endocrinol. (Kbh) *47*:419-432 (Nov.) 1964.
4. Liddle, G. W.: Arch. Intern. Med. *102*:998-1004 (Dec.) 1958.
5. Liddle, G. W.: Ann. N.Y. Acad. Sci. *139*:466-470 (Nov. 22) 1966.

See following page for brief summary.

To help control the aldosterone factor in essential hypertension

Aldactazide®

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Indications—Hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusion may benefit from Aldactazide therapy.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of the renal function. Anuria; sensitivity to thiazides or other sulfonamide-derived drugs. Probably contraindicated in acute or severe hepatic failure.

Warnings—Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Potassium supplementation is recommended only in exceptional instances, but may be considered when a glucocorticoid is also given. Utilize normal dietary sources of potassium if possible when potassium supplementation is necessary. If enteric-coated potassium is used be alert to the possible development of hemorrhagic, stenotic, ulcerated or perforated small-bowel lesions; deaths have occurred. The possibility of exacerbation or activation of systemic lupus erythematosus by sulfonamide derivatives, including thiazides, has been reported.

Administer thiazides with caution to pregnant or lactating patients. Adverse reactions which may occur in the adult (hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, etc.) may possibly occur in the newborn, since thiazides cross the placental barrier and may also appear in breast milk.

Precautions—Consider the possibility of fluid and electrolyte imbalance. Serum and urine electrolyte determinations are particularly important in patients with excessive vomiting or in those receiving fluids parenterally. Medications such as digitalis may also influence serum electrolytes. Warning signs of possible fluid and electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains, cramps or fatigue, hypotension, oliguria, tachycardia, gastrointestinal symptoms. Hypokalemia may develop with brisk diuresis in severe cirrhosis or during the concomitant use of glucocorticoids or ACTH. Inadequate oral electrolyte intake contributes to hypokalemia. Hypokalemia may cause signs of digitalis intoxication with previously tolerated doses of digitalis.

Give Aldactazide cautiously to patients with severe liver disease since thiazides can precipitate hepatic coma; discontinue if mental confusion increases. Consider also other factors that may precipitate hepatic coma, including blood in the gastrointestinal tract or preexistent potassium depletion. Reversible elevation of NPN and BUN may occur in some patients receiving Aldactazide. The most common electrolyte disturbance is dilutional hyponatremia which requires appropriate corrective measures. A true low-salt syndrome is rare; discontinue Aldactazide and administer sodium for this condition.

Although rare, the most potentially serious electrolyte disturbance is hyperkalemia; if this occurs discontinue Aldactazide and restrict potassium intake. Rarely, fatality due to hyperkalemia has been reported. Hyperkalemia is more likely to occur in severely ill patients with relatively small urine output or in patients receiving supplemental potassium; determine serum electrolytes frequently in such patients. Consider the possibility of hyperuricemia or a decrease in tolerance to glucose.

Patients with severely resistant edema may have an increased diuretic response following the addition of a potent glucocorticoid, such as 15 to 20 mg. of prednisone daily, to Aldactazide therapy. Supplemental potassium will usually be necessary in such patients and the usual precautions with glucocorticoids are necessary. Use caution if regional or general anesthesia is necessary since Aldactazide reduces vascular responsiveness to norepinephrine in such patients. Thiazides may increase responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in patients who have undergone sympathectomy.

Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may increase serum PBI levels without signs of thyroid disturbance.

Adverse Reactions reported with *spironolactone* use: Drowsiness and lethargy, mental confusion, diarrhea and other gastrointestinal symptoms, mild androgenic manifestations (including hirsutism, menstrual irregularity, deepening of the voice), gynecomastia, inability to achieve or to maintain erection, headache, maculopapular or erythematous cutaneous eruptions, urticaria, drug fever, ataxia.

Adverse reactions reported with *thiazide* use: purpura, thrombocytopenia, leukopenia, agranulocytosis, gastrointestinal disorders (anorexia, nausea, vomiting, diarrhea, abdominal cramps), rash, pruritus, paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, urticaria, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness, restlessness. Reduce dosage or withdraw drug whenever adverse reactions are moderate or severe.

Dosage and Administration—Dosage should be determined by individual titration. *For essential hypertension* the daily *adult* dosage is two to four tablets in divided doses; continue treatment for two weeks or longer. Adjust the dosage according to the response of the patient. Reduce the dosage of other antihypertensive agents, particularly ganglionic blocking agents, by 50 percent since Aldactazide potentiates the action of such drugs. *For edema, ascites or effusion in adults* the average dosage is one tablet 4 times daily; dosage may range from 1 to 8 tablets daily in divided doses. The daily dosage of Aldactazide *in children* should provide 0.75 to 1.5 mg. of Aldactone® (spironolactone) per pound of body weight.

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Computerized System for Noninvasive Techniques

I. Its Value for Systolic Time Intervals

SAMUEL ZONERAICH, MD, FACC
OLGA ZONERAICH, MD
JOHN RODENRYS, MS

Jamaica, Queens, and Stony Brook, New York

A total computerized system for the study of the noninvasive techniques and especially for external systolic time intervals is presented. Heart rate, left ventricular ejection time index (LVETI), Q–S_2 I (electromechanical index), preejection period (PEP), PEP/LVET ratio, isovolumic contraction time corrected for pulse transmission (ICTc), electromechanical interval (EMI), mechanical systole (S_1–S_2), DA/DT (quantitative apex cardiogram) and heart sounds were calculated from simultaneous recordings of electrocardiogram, carotid pulse and apex cardiogram by a multichannel, multifilter Cambridge MCIV phonocardiograph and by a CVA/94 unit MDS computer program.

A parallel study of these variables in 100 healthy persons by conventional manual calculations made from the Cambridge recordings and by the CVA/94 MDS computer system revealed identical results. The computerized system could more rapidly and accurately calculate many variables for systolic time intervals, thus offering the possibility for better evaluation of left ventricular function. Regression equations in relation to heart rate were found only for Q–S_2 = 520.4 − 1.79 heart rate; LVET = 417.5 − 1.59 heart rate; and S_1–S_2 = 435.7 − 1.58 heart rate. ICTc and EMI differences were negatively correlated at the $P = 0.001$ level. LVETI and Q–S_2 correlated positively at the $P = 0.01$ level. DA/DT reflecting quantitative apex cardiography could be calculated only by computer.

An extensive search for the potential usefulness of noninvasive methods in cardiology has been made in this laboratory[1–5] and others during the last few years. Data have been accumulated on the duration of various phases of cardiac systole by using simultaneous external polycardiographic techniques. The durations of these phases, when studied by noninvasive methods, were found to be altered in many abnormal cardiac states.

The use of systolic time intervals has been criticized because the regression equation in relation to heart rate varies widely in normal control subjects as studied by various groups and because there are problems of methodology and experimental design.[6] A review of normal values for systolic time intervals compiled from 14 original papers[7–20] indicates the wide range of these variables in normal subjects (Table I).

The purpose of this study was (1) to determine the usefulness of a rapid computer analysis for the measurement of systolic time intervals; (2) to eliminate human error in a parallel study by comparing the data obtained from conventional high fidelity equipment and manual measurements, with those obtained by a computerized system; (3) to calculate, through a computerized system, a large number of known variables, for a better and broader evaluation of left ventricular function; and (4) to compute new variables, not obtainable by conventional means.

From the Department of Medicine, Division of Cardiology, Queens Hospital Center, Long Island Jewish-Hillside Medical Center, Clinical Campus of the School of Medicine, State University of New York at Stony Brook, Stony Brook, N. Y.
Manuscript accepted August 9, 1973.
Address for reprints: Samuel Zoneraich, MD, Division of Cardiology, Queens Hospital Center, 82-68 164 St., Jamaica, Queens, N. Y. 11432.

TABLE I

Normal Values for Systolic Time Intervals in 14 Studies*

Authors	Subjects (no.)	Q–S_2	PEP	LVET	S_1–S_2	ICT	EMI	PTT (msec)
Weissler et al.[7]	211	(M) QS_2 = 2.1 HR + 546 ± 14 (F) QS_2 = 2.0 HR + 549 ± 14	0.4 HR + 131 ± 13 0.4 HR + 133 ± 11	(M) 1.7 HR + 413 ± 10 (F) 1.6 HR + 418 ± 10	...	...	...	...
Kumar & Spodick[8]	50	...	NC	376 − 1.2 HR ± 12	...	NC 70.9 ± 15.8	22 ± 9.8	...
Fabian et al.[9]	50	−159 + 503 HR ± 14	126 − 0.34 HR ± 12	389 − 1.41 HR ± 13	464 − 1.49 HR ± 16	70 ± 9.5	...	23
Diamant & Killip[10]	35	0.49 sec − 0.0017 × HR + 0.017	0.11 sec − 0.0003 × HR ± 0.015	0.38 sec − 0.0013 × HR ± 0.019	...	0.052 sec − 0.0002 × HR ± 0.015	...	...
Jain & Lindahl[11]	12	539 − 2.00 HR ± 15.9	...	...	...	...	...	...
Hamosh et al.[12]	42	−0.020 × HR + 0.522	−0.0004 × HR + 0.0126	−0.0016 × HR + 0.394	...	...	...	...
McConahay et al.[13]	33	Weissler et al.	Weissler et al.	Weissler et al.	...	Diamant & Killip	...	...
Chaitiraphan & Goldberg[14]	...	...	...	Weissler et al.	...	...	...	...
Tavel et al.[15]	27	...	...	Identical to Weissler et al.	...	...	...	...
Heikkila et al.[16]	139	Weissler et al.	Weissler et al.	Weissler et al.	456 − 1.8 HR ± 15	65 − 0.17 HR ± 12	...	...
Hodges et al.[17]	40	2.33 HR + Q–S_2	NC HR 90 ± 2.3	−2.22 HR + −443.7	...	...	...	...
Whitsett & Goldberg[18]	...	...	...	Weissler et al.	...	...	...	...
Austin et al.[19]	10	...	...	...	...	52.4 ± 14.9	24.7 ± 10.2	...
Lindquist et al.[20]	21	−1.85 HR + 502 ± 16	−0.44 HR + 117 ± 9	−1.42 HR + 385 ± 12	...	−0.07 HR + 32 ± 10	...	...

Because of different characteristics of phonocardiographic machines, several groups established their own normal values. Other groups used formulas established by one or two investigators. EMI = electromechanical interval; HR = heart rate; ICT = isovolumic contraction time; LVET = left ventricular ejection time; NC = no correlation with heart rate; PEP = preejection period; PTT = pulse transmission time; Q–S_2 = electromechanical systole; S_1–S_2 = mechanical systole.

Material and Methods

One hundred ambulatory, nonhospitalized persons, ranging in age from 17 to 62 years (mean 36.6), with no history of heart disease were included in this study. The number of men and women was almost equal.

All subjects had a normal history, normal cardiovascular system on clinical examination, normal electrocardiogram, a systolic pressure of 140 mm Hg or less and a diastolic pressure of 90 or less. They were receiving no medication. The studies were performed at approximately the same time (early in the morning).

The subjects were placed in the left lateral decubitus. During held expiration a 10 second recording was made of simultaneous apex cardiogram, carotid pulse tracing, phonocardiogram and lead II electrocardiogram with a Cambridge multichannel MCIV recorder and immediately after with the Medical Data Systems (MDS) CVA/94 unit (Medical Data Systems, Inc., San Diego, Calif.) (Fig. 1). 1-665 Cambridge pulse transducers with a time constant of 3.5 seconds were used to record the apex cardiogram and carotid pulse (funnel shape pick-up). A Cambridge 2100-4 microphone was used to record the phonocardiogram. The paper speed was 100 mm/sec. A Cambridge 1-206, five lead cable was used to record lead II of the electrocardiogram.

The MDS system utilized a Hewlett-Packard 21050 to record the carotid pulse and a single direct contact microphone 21050 A to record the apex cardiogram and phonocardiogram. A Hewlett-Packard 14056-B, three lead electrocardiographic cable was used to record lead II. After verification of proper signal placement, using the oscilloscope monitor on the CVA/94 cart, a simultaneous 10 second recording was made on the CVA/94 strip chart and on the magnetic tape using a frequency modulation (FM) recording technique.

Intervals

The following variables were computed with the CVA/94 computer program and, conventionally, by MCIV Cambridge recording:

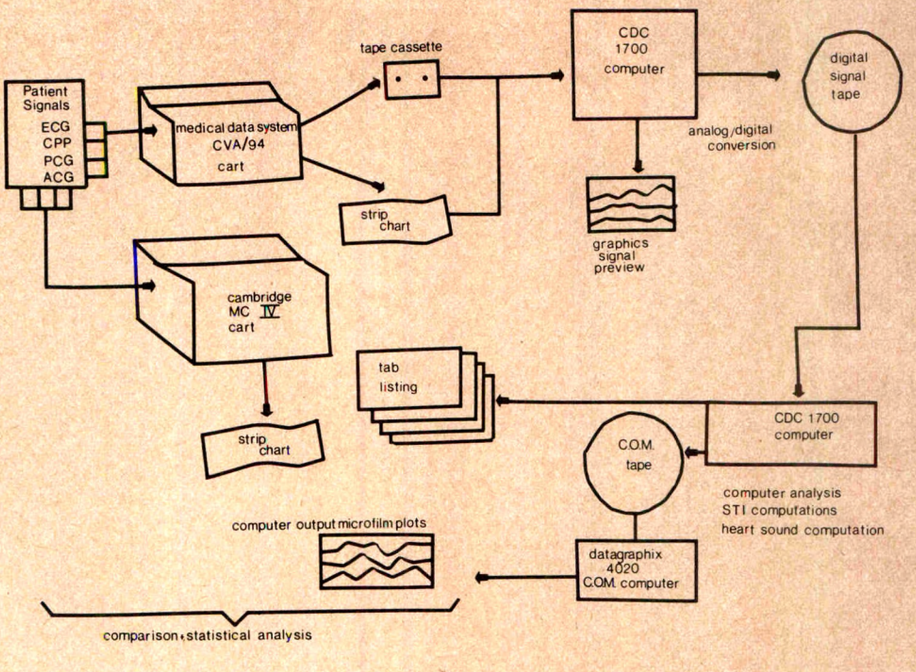

FIGURE 1. Schematic drawing of flow of patient signals during study using recordings and data processing performed by the Cambridge recorder and conventional calculation and by the CVA/94 unit MDS computer system. ACG = apex cardiogram, CPP = carotid pulse; ECG = electrocardiogram; PCG = phonocardiogram.

Heart rate: R–R interval (beats/min).

Left ventricular ejection time index (LVETI): carotid upstroke to trough of carotid incisura, corrected for heart rate.

Electromechanical systole index (Q–S_2 I): Q wave of the electrocardiogram to the aortic component of the second heart sound, corrected for heart rate.

Preejection period (PEP): Q wave to leg of upstroke of the carotid pulse, corrected for pulse transmission time.

Electromechanical interval (EMI): Q wave to upstroke of apex cardiogram.

Isovolumic contraction time, corrected for pulse transmission time (ICTc): (a) leg of upstroke of apex cardiogram to leg of upstroke of carotid pulse, corrected for pulse transmission time; (b) (leg of apex cardiogram to second heart sound) minus left ventricular ejection time.

PEP/LVET: ratio of preejection period to left ventricular ejection time.

Quantitative apex cardiogram (DA/DT) (calculated only by computer): ratio of the relative excursion of the apex cardiogram from leg of upstroke to the point of maximal slope (rate of change of apex cardiogram) divided by the interval between the Q wave of the electrocardiogram and the time of maximal slope.

Manual Analysis

Manual calculations of the systolic time intervals obtained with the Cambridge MCIV recording were read to the nearest 5 msec for 10 consecutive cycles. The rate-dependent raw values were corrected for heart rate and then averaged to obtain a representative value. Raw values that were not rate-dependent were directly averaged to obtain a representative value.

Computer Processing

The recordings made on the magnetic tape were processed by computer in two stages: (1) analog to digital conversion, and (2) CVA/94 computer program analysis.

The analog to digital conversion was performed on a CDC 1700 computer. The analog tape cassettes were played back into the CDC 1700 computer through an analog tape recorder and the signals digitized at the rate of 1,000 times/sec for 10 seconds. After analog to digital conversion, an interactive graphics monitor was used to display the digital signals. A check was made at this time for artifactual or missing signals. After verification of satisfactory signals, the patient's signals were written on digital magnetic tape.

The CVA/94 computer program analysis was performed on a CDC 1700 computer using the digital magnetic tape that was previously written. During the processing, 10 consecutive cardiac cycles were analyzed. The computer performed two basic functions; detection of heart sounds and computation of systolic time intervals. During the computer analysis, all rate-dependent intervals were converted into their respective indexes. At the completion of processing, a 45 line printer and a computer output microfilm (C.O.M.) tape were generated. In addition, 700 items of information on each patient were printed on the line printer for the basic reference file.

The C.O.M. tape was taken to a Datagraphic X4020 C.O.M. computer which produced graphs of the original signals of the patients (Fig. 2 and 3) with computer-generated annotations. These plots are for physician review of configuration and computer accuracy. The graphs are stored on microfilm and 11 by 11 bond paper. Normal values for the interval are printed by the computer for comparison.

The computer program also provides data on the time of occurrence of the following heart sounds: systolic clicks, aortic component of the second heart sound (A_2), opening snap, third (S_3) and fourth (S_4) heart sounds and the mitral component of the first heart sound (S_1).

Comparison and Statistical Analysis

During the statistical comparison, the data from the Cambridge tracings and the Medical Data Systems computer program were assumed to be from two different populations. A Student t test for the differences between the means of two variables was performed. A correlation study,

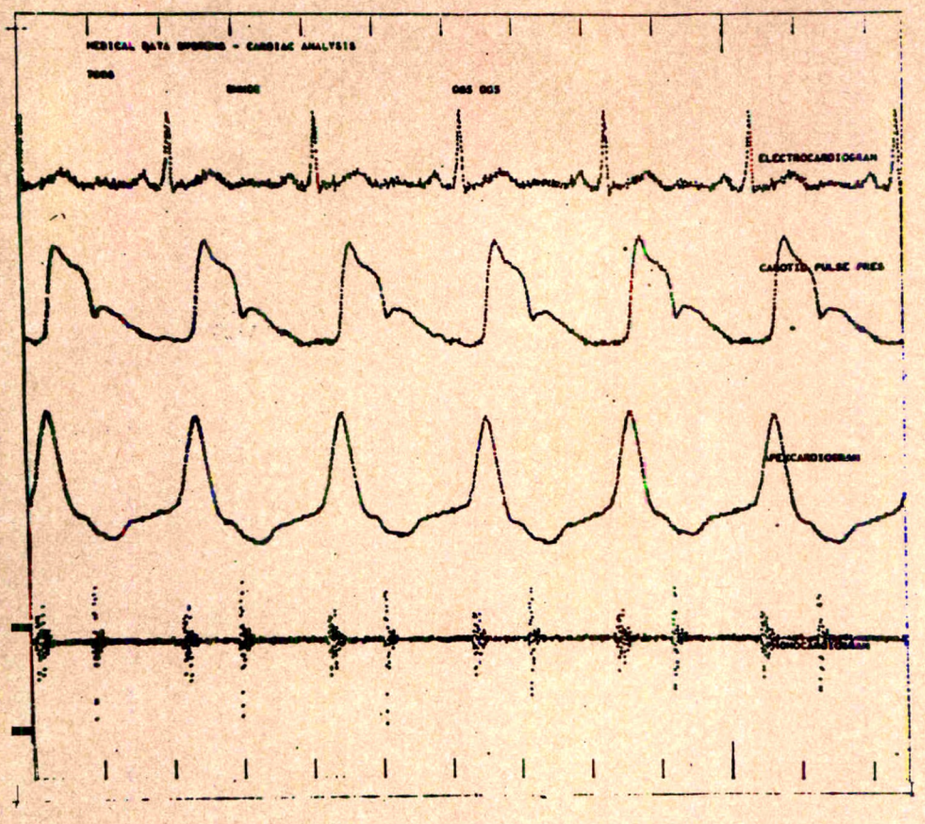

FIGURE 2. Computer graphs of the original patient signals. **From top to bottom:** electrocardiogram, carotid pulse tracing, apex cardiogram and phonocardiogram. Numbers at top identify patient's code number, hospital code number and tape file index.

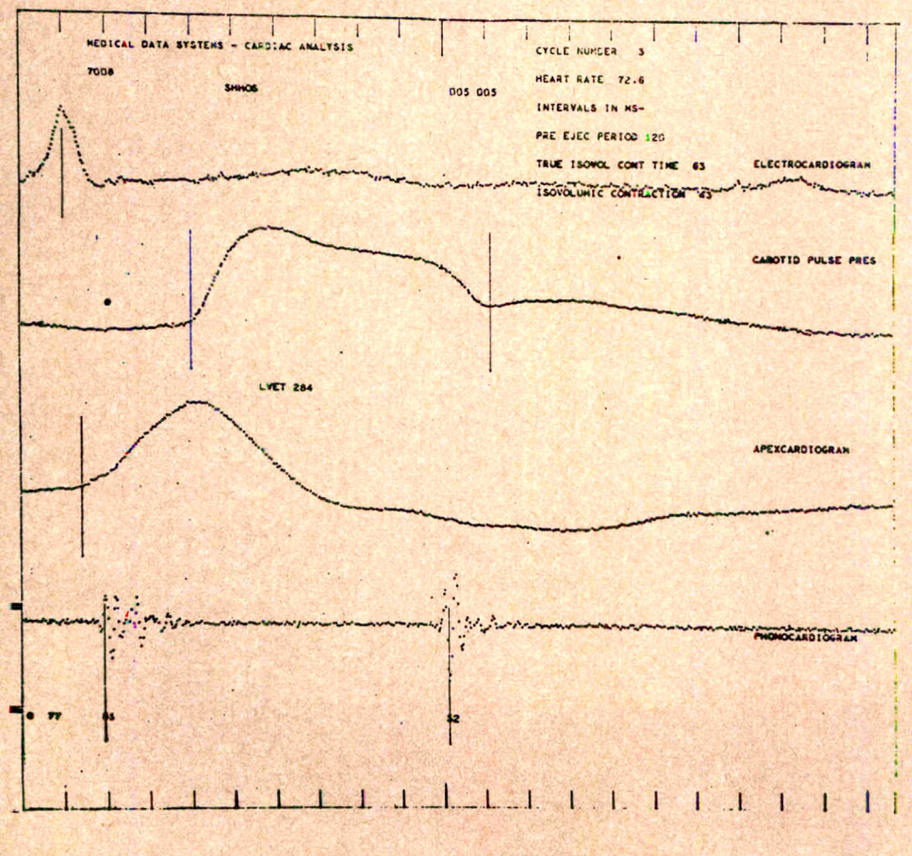

FIGURE 3. Computer analysis of one cardiac cycle. The figures are registered on the chart. **From top to bottom:** electrocardiogram, carotid pulse tracing, apex cardiogram and phonocardiogram. The patient's code number, hospital code number, tape file index and both the first and second heart sounds are indicated. Values are shown for cycle number, heart rate, preejection period, true isovolumic contraction time, isovolumic contraction time and left ventricular ejection time (LVET).

using the null hypothesis, was also performed to determine the relation between the differences of the variables.

Results

As shown in Table II, none of the differences between the manual and the computer results were significant (6 values were at the $P = 0.50$ level and 1 was at the $P = 0.30$ level), indicating that the computer system was almost duplicating the results obtained by manual, conventional calculation of the Cambridge recorded signals.

The results indicate only two significant relations among the differences. Differences for isovolumic contraction time, corrected for pulse transmission time (ICTc), correlated negatively with each other at the $P = 0.001$ level. This is an expected finding, since a prolonged ICTc interval will shorten the electromechanical interval and vice versa. Left ventricular ejection time index and Q–S_2 were positively correlated at the $P = 0.01$ level. This correlation probably results from a subjective bias of selecting the component of the second sound that is closest to the incisura in reading the charts manually.

There was no relation between preejection period and heart rate. Therefore no linear regression formula was calculated for the former variable.

ICTc was calculated for comparison by two methods: (1) from leg of the upstroke of the apex cardiogram to leg of the upstroke of the carotid pulse corrected for pulse transmission time, and (2) (leg of the apex cardiogram to S_2) minus left ventricular ejection time. The results indicated that the first method showed less scatter and a lower standard deviation. Thereafter, the first method was used routinely.

Discussion

Our study clearly demonstrates that many of the disadvantages of using systolic time intervals could be avoided by using better techniques of recording and calculating these intervals. Our approach for recording multiple variables is based on theoretical and practical considerations indicating that no single measure has proved to be of unchallenged superiority in evaluating left ventricular function and that the interpretation of results obtained by any method must be qualified by recognition of the limitations of the technique.

It is important to realize that the early vibrations of the first heart sound[21,22] are occasionally difficult to identify for calculation of isovolumic contraction time, that the latter may increase the value of preejection period as a measure of left ventricular performance and, finally, that newer variables such as electromechanical interval and DA/DT may reflect significant events in the cardiac cycle.

Use of the apex cardiogram for the calculation of isovolumic contraction time diminishes the wide variability encountered in the normal population when measurements for this variable are based on the identification of a high vibration in the first heart sound. Recording of the apex cardiogram requires minimal experience. Poor or unobtainable tracings due to obesity, chronic lung disease or other causes occur in less than 10 percent of recordings in our experience. Minimal arterial distortion resulting from filtering and information gain are occasionally encountered in obese subjects when the arterial pulse is recorded.[23]

Our data indicate that the preejection period could not be corrected for heart rate, since heart rate has a

TABLE II

Comparison of Manual Results with Results Obtained with Computer System (msec)

Variable*	Regression Equation	Manual Results	Computer Results	Difference	*t* Value	Probability
QS_2I	520.4 − 1.79(HR) (no. = 93; $r = -0.68$)	520.0 ± 20.8	518.7 ± 16.6	±1.3	0.43	$P > 0.50$
LVETI	417.5 − 1.59(HR) (no. = 93; $r = -0.67$)	417.0 ± 19.4	414.0 ± 15.7	+3.0	1.05	$P < 0.30$
PEP	Not significant (no. = 93; $r = -0.11$)	88.5 ± 16.9	88.1 ± 12.9	+0.4	0.17	$P > 0.50$
ICTc	Not significant (no. = 93; $r = -0.11$)	65.9 ± 14.8	66.4 ± 12.6	−0.5	0.23	$P > 0.50$
EMI	Not significant (no. = 93; $r = -0.15$)	24.1 ± 7.2	24.5 ± 4.3	−0.4	0.44	$P > 0.50$
S_1–S_2	435.7 − 1.58(HR) (no. = 93; $r = -0.65$)	435.2 ± 20.2	437.0 ± 16.5	−1.8	0.61	$P > 0.50$
PEP/LVET	Not significant (no. = 93; $r = -0.16$)	0.291 ± .064	0.287 ± 0.55	+0.004	0.42	$P > 0.50$
DA/DT	Not significant (no. = 93; $r = -0.09$)	.....	26.1 ± 13.1	...	...	...

*Mean pulse transmission time was 28.5 msec.

DA/DT = quantitative apex cardiogram; EMI = electromechanical interval; ICTc = isovolumic contraction time corrected for pulse transmission; LVETI = left ventricular ejection time index; PEP = preejection period; PEP/LVET = ratio of preejection Period to left ventricular ejection time; QS_2I = electromechanical systole index; S_1–S_2 = mechanical systole.

minimal effect on its duration.[24] The same is true for isovolumic contraction time. The linear regression equation for left ventricular ejection time obtained by us is similar to that found by Weissler et al.[7]

Isovolumic contraction time calculated from the leg of the upstroke of the apex cardiogram to the leg of the carotid upstroke is easily identifiable from simultaneous recordings of the apex cardiogram and carotid pulse. The beginning of the ejection period could not be calculated from the apex cardiogram alone by conventional methods of calculation, since it is difficult to identify the beginning of the ejection period that occurs before the E point of the apex cardiogram.[8] Instead, the real beginning of the ejection period calculated from the upstroke of the apex cardiogram alone was obtained only by computer.

DA/DT identified a fraction of the preejection period, corresponding to the upstroke of the first derivative of the apex cardiogram and considered to be similar to the first derivative of the left ventricular pressure.[25] The magnitude of the first derivative of the apex cardiogram has been considered to be proportional to the velocity of motion of the left ventricular wall and related to the functional status of the myocardium.[26]

The interval between the onset of ventricular depolarization and the preejection peak of the first derivative of left ventricular pressure, suggested by Mason et al.[27] as an index of left ventricular function, has been correlated by Vetter et al.[28] with the interval between the onset of ventricular depolarization and the preejection peak of the first derivative of the apex cardiogram. Statistically significant correlations were obtained with ejection fraction, left ventricular end-diastolic pressure and left ventricular end-diastolic volume. The data obtained by this group support the use of quantitative apex cardiography for screening of serial clinical studies of left ventricular function.

Advantages of Computerized System

Computing systems have been used for noninvasive techniques in the past by Freis and Kyle,[29] who recorded the carotid and brachial pulses on magnetic tape, plotted the curves with a computer and then manually identified the time intervals. Eddleman[30] analyzed the precordial pulsations by normalized plots of kinetocardiograms. Golde and Burstin[31] manually calculated systolic time intervals in normal children, stored the obtained data on magnetic tape and used an IBM 360-50 computer for statistical analysis. Our computerized system for the first time eliminates any manual identification for calculations of variables of systolic time intervals.

The advantages of fast and accurate calculations are evident. Evaluation of left ventricular performance, which requires the use of many variables and is difficult to measure manually, can easily be calculated by the computing system. DA/DT as an expression of quantitative apex cardiography, for evaluation of left ventricular function, could be identified by the computer from the apex cardiogram alone.

Graphic computer output at a ratio of more than 1,000 msec permits analysis of individual heart sound components and timing relations. Printed computer output provides computation for up to 10 cardiac cycles and performs automatic correction for rate-dependent variables.

Reliable data obtained by conventional high fidelity phonocardiographic equipment are almost identical to those obtained by the computing system (Table II) and confirms the validity of ratios and variables conventionally obtained by external measurements of systolic time intervals. The hemodynamic factors involved in determining the systolic time intervals are now better recognized. Simultaneous measurements of intracardiac dynamics have demonstrated close parallelism between direct and indirect measurements[32] of systolic time intervals. Externally recorded systolic time intervals are used on a large scale for the evaluation of left ventricular performance in man in acute and chronic cardiovascular disease.

The use of the computerized system offers several distinct advantages over the present conventional recording system. By following precisely defined algorithms and computing first derivatives, the computer eliminates subjective variability in the identification of events in the cardiac cycle. This is particularly important in the identification of muffled heart sounds and slurred pulse wave upstrokes. The significant increase in accuracy (1 msec compared to 5 msec with conventional recordings) obtainable with the computer system should reduce the present variances and overlapping results obtained from the calculation of systolic time intervals calculated by different observers.

Individual position assessment of the morphologic aspects of the tracing is facilitated by the high graphic output speed used in the display of the tracings and by the printed computation covering 10 heart cycles. The greatest potential advantage of the computerized system lies in its ability to calculate quickly more sophisticated variables related to contractility from externally measured tracings. The use of these variables, difficult to measure manually, could lead to a better evaluation of left ventricular performance.

Acknowledgment

We thank Mr. Floyd Jackson for his assistance with photography, Miss Ada Fantroy for her technical assistance and Mrs. Karen Franklin for her secretarial assistance.

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Quantification of Serum Creatine Phosphokinase Isoenzyme Activity

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Three serum creatine phosphokinase (CPK) isoenzymes (MM, MB and BB) have been recognized. Myocardium is richly endowed with MB CPK. Accordingly, increased serum MB CPK activity reflects myocardial injury. Although recent advances have facilitated detection of activity of CPK isoenzymes, available techniques have unavoidable quantitative limitations. Accordingly, we used a new procedure to quantify CPK isoenzymes in serum samples with normal or increased total CPK activity. Samples were diluted or concentrated so that total CPK activity was 0.100 to 1.200 IU/ml and then subjected to electrophoresis on cellulose acetate. Regions of the strips encompassing each isoenzyme were cut out, immersed in 0.5 to 3 ml of assay medium in which the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) was generated as a function of isoenzyme activity. NADPH was detected by serial determinations of fluorescence in the medium. The assay was linear with respect to time and isoenzyme activity (0.010 to 1.2 IU/ml, no. = 100) and recovery averaged 83 ± 1.8 percent (standard deviation). Reproducibility was within 2 percent. Accuracy of the method was validated with selected mixtures of BB and MM isoenzymes. Serum MB CPK activity averaged only 0.002 ± 0.001 IU/ml in normal persons (no. = 27), compared to 0.064 ± 0.043 IU/ml in 30 patients with myocardial infarction. Serum MB CPK activity was not increased in 23 patients after intramuscular injections or abdominal surgery. The procedure described permits quantitative determination of activity of individual CPK isoenzymes in serum samples with or without increased total CPK activity and thus is of potential value in the quantitative assessment of myocardial infarction by serum enzyme analysis.

Serum creatine phosphokinase (CPK) determinations are becoming increasingly important in the diagnosis[1] and quantification[2–4] of acute myocardial infarction. Three serum CPK isoenzymes, each a dimer (MM, MB, and BB), have been recognized. Extracts of human myocardium contain both MB and MM in contrast to extracts of skeletal muscle, which contain primarily MM. Thus, ischemic myocardial injury is reflected by increased serum MB activity.[5–7] Recent improvements in procedures for assay of CPK isoenzyme activity involve separation of isoenzymes by electrophoresis and scanning of the electrophoretic medium to detect fluorescence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH).[5,8] However, quantitative results obtained with all methods dependent upon scanning tend to be inaccurate for several reasons[9,10]: (1) Isoenzymes may be distributed asymmetrically in the electrophoretic supporting medium so that selection of the position used for scanning may influence results. (2) Activity of individual isoenzymes may be underestimated because of limited diffusion of substrate into the supporting medium or loss of NADPH or dye from the medium. (3) Apparent activity of specific isoenzymes may deviate from linearity with respect to time or

From the Department of Medicine, University of California, San Diego, La Jolla, Calif. and the Department of Medicine, Washington University, St. Louis, Mo. This research was supported in part by U. S. Public Health Service Myocardial Infarction Research Unit Contract PH 43-68NHLI-1332, and National Heart and Lung Institute U. S. Public Health Service Research and Career Development Award (1-K4-HL-50, 179-01) (Dr. Sobel), and Ontario Training Grant and Ontario Heart Foundation (Dr. Roberts). Manuscript accepted September 5, 1973.

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actual activity because of disparate activities of one or more isoenzymes in a mixture. Accordingly, we developed and evaluated a procedure for quantitative analysis of CPK isoenzymes designed to eliminate these difficulties and used it to measure activity of CPK isoenzymes in serum from hospitalized subjects with and without acute myocardial infarction.

Methods

Blood samples were collected in 0.010 molar neutralized EGTA, and serum was separated by centrifugation. Supernatant fractions of 16,000 g were prepared from human papillary muscles obtained freshly during the course of mitral valve replacement, and from brain obtained at autopsy.[3] Total CPK activity was measured spectrophotometrically after samples were diluted with 0.01 molar Tris, pH 7.4 containing 0.2 percent bovine serum albumin (Tris-BSA), so that CPK activity was approximately 0.1 IU/ml and thus within the limits of linearity of the assay.[11] CPK isoenzymes were separated by cellulose acetate electrophoresis.[7,12] Samples were diluted with Tris-BSA or concentrated with Aquaside II (Calbiochem) to produce total CPK activity values of 0.100 to 1.200 IU/ml. Control experiments were performed by omitting creatine phosphate as substrate.

In preliminary experiments (see Results) we found that detection of electrophoretically separated isoenzymes by fluorescence scanning[5,8] was inadequate for quantification. *Accordingly, the following approach was employed:*

1. CPK isoenzymes were separated by cellulose acetate electrophoresis.

2. After electrophoresis, sections of the cellulose acetate strips containing each isoenzyme were cut out, immersed in 0.5 to 3 ml of the CPK assay medium in a disposable cuvette, and incubated at 25° C with constant shaking. Incubation time and volume were chosen to provide linear reaction rates and sufficient fluorescence from NADPH generated by isoenzymes on each selected portion of the strip. Analysis of 100 samples each of sections containing the three isoenzymes indicated that the enzymes were contained within the following regions: MM, 4 mm cathodal to 12 mm anodal; MB, 12 mm anodal to 37 mm anodal; BB, 37 mm anodal to 47 mm anodal.

3. NADPH generated was detected by serial measurement of fluorescence in the aqueous medium in which the selected portions of the cellulose acetate strips were being incubated.

To determine whether NADPH was eluted quantitatively under these conditions we applied 10 μl aliquots of samples containing known quantities of NADPH to moist cellulose acetate membranes, allowed the samples to dry for 15 minutes, eluted the NADPH from the strips under the same conditions as those used in the isoenzyme assay procedure and determined fluorescence in the aqueous medium with use of spectrophotometry.

To determine whether the isoenzyme assay was linear with respect to time and enzyme activity, aliquots of rabbit skeletal muscle CPK were applied to cellulose acetate strips but not separated by electrophoresis. Selected regions of the strip were cut out and incubated in CPK reaction medium. Fluorescence in the aqueous medium was determined serially with an Aminco-Bowman fluorometer while the cellulose acetate strip was removed transiently from the solution.

To assess recovery of isoenzyme activity from cellulose acetate strips, fluorescence detected with aliquots added to the medium itself was compared with fluorescence detected when corresponding aliquots were assayed in cellulose acetate strips immersed in incubation medium.

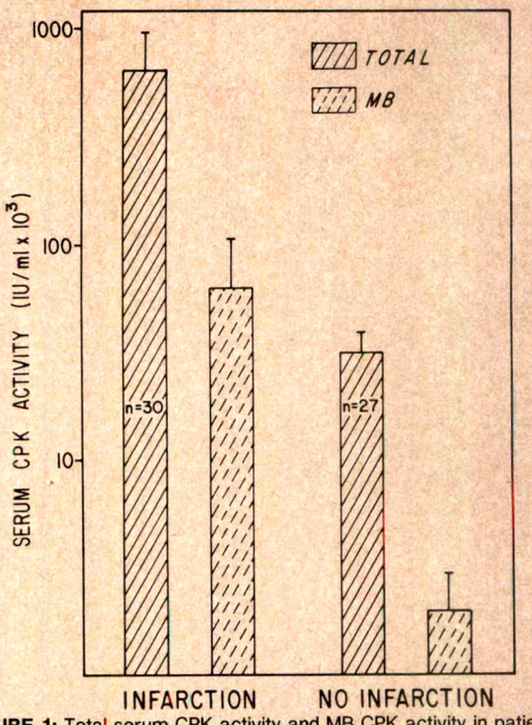

FIGURE 1: Total serum CPK activity and MB CPK activity in patients with myocardial infarction and in hospitalized patients without infarction. CPK activity and MB CPK activity were assayed in samples obtained from patients with myocardial infarction and selected on the basis of peak CPK activity for each patient. Results expressed represent means plus 1 standard deviation indicated by the vertical bars. Serum MB CPK activity in patients with infarction averaged 0.064 IU/ml, compared with 0.002 IU/ml in samples from hospitalized patients without infarction.

To determine whether electrophoresis altered recovery of CPK activity, aliquots of rabbit skeletal muscle CPK were subjected to electrophoresis before fluorometric assay of CPK activity in appropriate regions of the cellulose acetate membrane. Percent recovery was calculated by comparison with activity observed when corresponding aliquots were assayed in solution. Recovery of MM and MB isoenzymes in serum samples was determined in the original sample and in serial dilutions.

Reliability of the assay was examined with human myocardial supernatant fractions containing MM and MB CPK. Activities of each were determined 10 times from aliquots of the initial sample and 10 times each from aliquots of the sample diluted to contain 0.2 and 0.1 IU/ml.

Accuracy of the method was assessed with solutions formulated with selected quantities of BB and MM isoenzymes.

Case material: Isoenzymes were assayed quantitatively in serum samples containing MM and MB isoenzymes and increased total CPK activity from 30 patients with acute myocardial infarction, 27 patients without infarction and normal total CPK activity, 23 patients with elevated total CPK activity after intramuscular injections (16 patients) and abdominal surgery (7 patients). Isoenzymes were assayed also in 16 skeletal muscle extracts obtained at operation or at autopsy.

TABLE I

Total CPK and CPK Isoenzyme Activity in Serum Samples and Skeletal Muscle Extracts (means ± 1 standard deviation)

Category and no.	Total CPK	MM CPK	MB CPK
	A. Serum Samples (IU/ml)*		
Hospitalized control subjects (27)	0.036 ± 0.013	0.033 ± 0.012	0.002 ± 0.001
Patients with acute myocardial infarction (30)	0.860 ± 0.120	0.797 ± 0.112	0.063 ± 0.043
Patients receiving intramuscular injections (deltoid)			
Diazepam (5)	0.454 ± 0.051	0.451 ± 0.052	0.003 ± 0.001
Morphine sulfate (7)	0.347 ± 0.089	0.345 ± 0.089	0.003 ± 0.002
Ampicillin (4)	0.595 ± 0.121	0.593 ± 0.121	0.002 ± 0.001
Patients undergoing abdominal surgery (7)	1.024 ± 0.232	1.022 ± 0.232	0.003 ± 0.002
	B. Skeletal Muscle Extracts (IU/g)†		
Obtained at autopsy (10)	2.630 ± 0.260	2.630 ± 0.260	0
Obtained at operation (6)	1.430 ± 0.080	1.430 ± 0.000	0

* Serum samples analyzed were those exhibiting peak total CPK in patients who had serial samples obtained at 3 hour intervals.

† Extracts of skeletal muscle were prepared as 1:25 homogenates in 0.25 M sucrose, 1 mM EGTA and 10 mM potassium phosphate buffer, pH 7.4. Total CPK and CPK isoenzymes were assayed in 16,000 g supernatant fractions. Tissue samples were obtained from the rectus abdominis muscle in patients undergoing abdominal surgery and from the deltoid, pectoralis major and psoas muscles in patients who had died 4 to 6 hours before the study.

In studies designed to determine the effects of storage media on preservation of isoenzyme activity, papillary muscle extracts were diluted with human serum, divided into aliquots and protected with 0.005 mercaptoethanol, neutralized 0.010 molar sodium ethyleneglycol tetraacetic acid (EGTA) or 2.5 molar sucrose or a combination of the three. Samples were frozen on dry ice and ethanol, stored at −20° C and assayed serially after fast thawing.

Results

MB and MM activity in serum samples: MM and MB activities in serum samples with peak total CPK activity from 30 patients with acute myocardial infarction and in serum samples from 27 patients without increased total serum CPK are shown in Figure 1. Both total CPK and MB CPK activity were increased in samples from patients with acute myocardial infarction. Furthermore, the average absolute activity of MB CPK was more than 20 times greater in samples from patients with infarction. Increased MB CPK activity after infarction has been identified in previous studies.[5,6,8,9] However, the sensitivity of the present method permits detection of some MB CPK in serum from patients without acute myocardial infarction who have normal total serum CPK activity.

Total serum CPK activity may increase after intramuscular injections or surgery, presumably because of release of CPK from skeletal muscle, and frequently the diagnosis of acute myocardial infarction must be considered in patients in this setting. Accordingly, we assayed CPK isoenzymes in samples with increased total CPK activity from hospitalized patients without myocardial infarction who had received intramuscular injections of diazepam, morphine sulfate or ampicillin. Total CPK, MB CPK and MM CPK activity in these samples are tabulated in Table I and compared with results in samples from patients who had recently had abdominal surgery or myocardial infarction. MB CPK activity was not appreciably increased in samples from patients after intramuscular injections or surgery even when total serum CPK values were as high as those in patients with acute myocardial infarction.

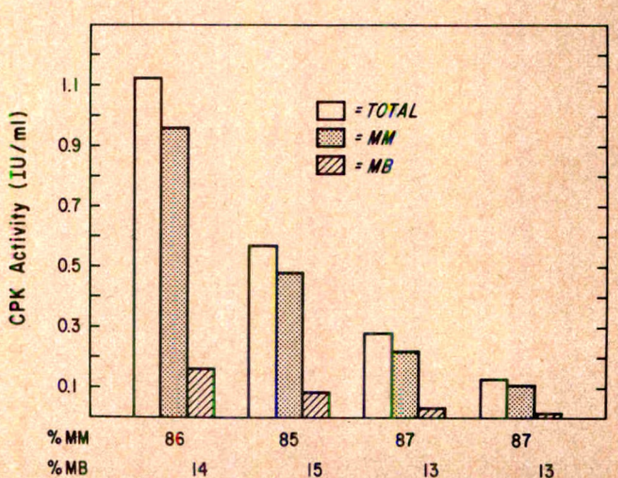

FIGURE 2. Activity of total serum CPK, MM CPK and MB CPK in aliquots from serial dilutions of the same initial serum sample. The proportion of MM and MB isoenzymes remained constant in aliquots from serial dilutions of the initial sample with total CPK activity levels ranging from 1.120 to 0.120 IU/ml. Results are averages of duplicate determinations with each dilution.

Both total CPK and activity of each isoenzyme (BB, MM, and MB) remained constant for at least 2 weeks when samples were stored with EGTA, mercaptoethanol or sucrose as described under Methods.

Evaluation of the quantitative method: Recovery of NADPH from cellulose acetate membranes ranged from 97.5 to 99.5 percent (no. = 10). Fluorescence increased linearly with time for at least 5 minutes in each case when CPK in rabbit skeletal muscle samples (0.010 to 1.2 IU/ml) was assayed after electrophoresis (no. = 100).

Average recovery was 97 ± 2.5 percent (standard deviation) (no. = 100) when rabbit skeletal muscle samples were applied to cellulose acetate but not separated by electrophoresis. After electrophoresis recovery was virtually constant, averaging 83 ± 1.8 percent (no. = 100). Determinations of MM activity after electrophoresis varied by ±3 percent (no. = 100 samples with activity of 0.010 to 1.2 IU/ml). Results with serial dilutions of serum samples containing more than one isoenzyme (Fig. 2) indicated consistent proportions of MB and MM CPK in aliquots with total CPK activity values ranging from 1.120 to 0.120 IU/ml.

When each of three papillary muscle extracts (MB CPK activity = 0.018, 0.037 and 0.256 IU/ml) was assayed 10 times, apparent activity of each isoenzyme varied by only ±1.5 percent (range). When selected mixtures of BB from human brain and MM CPK from rabbit skeletal muscle were assayed, the observed and expected values for each isoenzyme agreed within ±3 percent (three mixtures with respective total CPK activity levels of 0.2, 0.5 and 1.0 IU/ml).

Difficulties encountered with conventional scanning procedures: Although fluorescence scanning is a sensitive technique,[8,13] in our hands it had serious quantitative limitations. For example, when the fluorometer was used to scan five different positions on the same strip, the apparent MB CPK isoenzyme activity ranged from 12 to 38 mIU/ml. When aliquots of the same sample were applied to 10 different strips and each strip was subsequently scanned, the apparent activity of MB CPK in the sample ranged from 11 to 39 mIU/ml. When selected mixtures of BB and MM CPK were applied to eight different strips and fluorometric scanning was performed, the apparent ratio of BB to MM activity differed from that expected by 20 to 80 percent (no. = 8) despite vigorous efforts to apply the samples uniformly. In preliminary experiments (data not shown) in which electrophoresis was performed on agarose[5,8] rather than on cellulose acetate, we encountered similar difficulties. Thus, despite the sensitivity exhibited by fluorescence scanning, we found quantitative limitations that were minimized or avoided by the procedure used in this study.

Discussion

Increased total serum CPK activity is a hallmark of acute myocardial infarction. However, total CPK activity increases after intramuscular injections, trauma and in association with many disorders. Release of CPK from organs other than the heart could influence estimation of infarct size based on serum CPK analysis. Thus, quantification of serum CPK isoenzymes is of particular importance in delineating the source of CPK in serum.

Although fluorescence scanning has been useful for detecting CPK isoenzymes,[8] several factors may limit its value as a quantitative tool including (1) asymmetric distribution of isoenzymes along the axis of scanning,[9,10,13–15] (2) loss of NADPH from the electrophoretic medium,[16] (3) limitation of penetration of substrate into the supporting medium,[9,16] and (4) deviation of the reaction from linearity with respect to one or more isoenzymes in a mixture because of disparate activities of each.[9,16]

Advantages of method: The method described was designed to avoid these difficulties and to facilitate accurate quantitative determinations of the activity of each individual isoenzyme in samples containing a mixture. Since isoenzymes are assayed separately, reaction conditions can be adjusted to achieve linearity with respect to time and activity of each isoenzyme. All NADPH generated contributes to fluorescence since it is eluted into the aqueous reaction medium. Availability of substrate to each isoenzyme in the supporting medium is faciliated by constant shaking and immersion of the supporting medium into the reaction solution. The problem of nonuniform distribution of the sample is eliminated since the entire region of the supporting medium encompassing each isoenzyme is utilized. Reactions are performed kinetically. The method detects individual isoenzymes with an activity level of less than 0.002 IU/ml, and hence is capable of quantifying isoenzymes even when total serum CPK activity is not increased. Results appear to be reproducible.

Clinical application: The precision, accuracy and sensitivity of this method make it a potentially useful adjunct in delineating the source of CPK contributing to total serum CPK activity in patients and in quantifying myocardial injury by analysis of serial changes in activity of serum enzymes.[4] The technique should prove particularly useful in detecting and quantifying myocardial injury in patients with concomitant injury to skeletal muscle, such as those undergoing coronary bypass grafting and other surgical procedures.

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Prophylactic Quinidine for the Prevention of Arrhythmias After Acute Myocardial Infarction

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A selected group of 103 patients with uncomplicated myocardial infarction of less than 24 hours' duration were randomly assigned to two different treatments: 45 patients received quinidine sulfate orally in a dose of 0.4 g every 8 hours and 58 patients received sodium lactate placebo. The period of observation was 72 hours. Ventricular tachyarrhythmias, including ventricular tachycardia, and ventricular premature beats that were multifocal or occurred at a frequency greater than 5/min occurred in 26 of 58 patients (45 percent) receiving placebo and in 7 of 45 patients (16 percent) treated with quinidine. Quinidine effected an even more significant reduction of ventricular tachycardia; this arrhythmia was observed in 12 of 58 patients receiving placebo and in only 1 of 45 quinidine-treated patients ($P < 0.01$). Continuous 72 hour electromagnetic tape recordings showed no reduction in the frequency of isolated ventricular premature beats in the quinidine-treated group compared with the control group. Bradyarrhythmias including heart block warranted discontinuance of the trial in 6 of 45 quinidine-treated patients and 2 of 58 patients receiving placebo. There was no difference in mortality in the two groups during the 72 hour study period or during the entire period of hospitalization.

The advent of coronary care units together with the present treatment of ventricular arrhythmias is credited with reducing the mortality of patients admitted to the hospital with acute myocardial infarction.[1–4] Although the monitoring and emergency treatment facilities of coronary care units are becoming more widespread, they are not universally available. It has been stated[5] that 50 percent of patients entering the hospital with acute myocardial infarction in the United States are admitted to hospitals that have less than 200 beds and probably lack special monitoring facilities. It is attractive to consider that an oral antiarrhythmic agent administered to patients admitted to hospitals without coronary care facilities might reduce mortality from ventricular arrhythmia.

Quinidine sulfate, the prototype of antiarrhythmic agents, has been in clinical use for more than 50 years, principally for the reestablishment and maintenance of sinus rhythm after supraventricular arrhythmia. It has also been effective in the treatment of established ventricular tachycardia. Its pharmacologic action and clinical efficacy in the treatment of ventricular tachycardia naturally led to its trial in the prevention of ventricular arrhythmias, including ventricular premature beats.

Although in early studies[6–8] the use of quinidine was advocated for prevention of ventricular dysrhythmias after acute myocardial infarction, subsequent attempts to validate this approach by clinical therapeutic trials have yielded conflicting opinions. Thus, although some investigators have offered no support for such routine use of quinidine,[9–11] others[12–17] have suggested that this prophylactic approach

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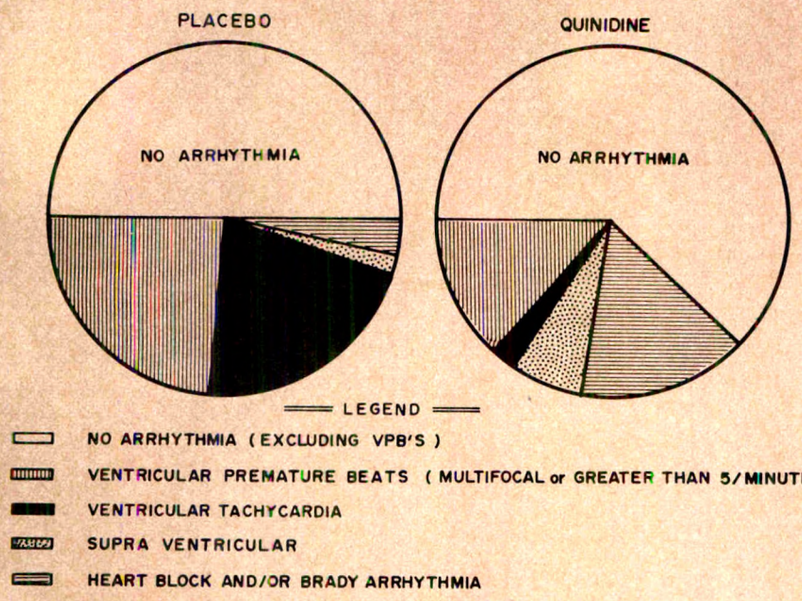

FIGURE 1. Relative frequency of arrhythmias after myocardial infarction in 58 patients receiving placebo and 45 receiving quinidine. Data exclude ventricular premature beats that were not multifocal or occurred less frequently than 5/min.

can reduce the frequency of ventricular dysrhythmia and sudden death. The desirability of an oral prophylactic antiarrhythmic agent, the encouraging results of animal studies, the conflicting evidence of earlier clinical trials and the availability of techniques for continuously monitoring patients who have recently had a myocardial infarction prompted this reappraisal of the value of orally administered prophylactic quinidine in myocardial infarction.

Methods

Case material: All patients admitted to the coronary care unit of Victoria Hospital from January 1968 until March 1970 were considered for inclusion in the study if they had experienced the onset of symptoms within the preceding 24 hours and were free from shock, acute congestive failure and serious arrhythmia. The arrhythmias excluding patients from the study were supraventricular tachycardia, ventricular tachycardia and ventricular premature beats that were multifocal or occurred with a frequency greater than 5/min. Patients found to have bundle branch block, atrioventricular (A–V) dissociation or a history of sensitivity to quinidine were also excluded.

During this period 538 patients were admitted, and 246 were considered suitable for the study. They were assigned randomly[18] to treatment by quinidine or placebo, with use of a double blind protocol. This procedure was considered desirable to avoid influence on the nursing staff and physicians in interpreting the electrocardiograms monitored in the coronary care unit and in later reviewing the continuous electrocardiogram recorded on magnetic tape in each patient for 72 hours or until his removal from the study.

Patients were continued in the study and included in the final evaluation only if the diagnosis of acute myocardial infarction was confirmed by the following criteria: (1) typical cardiac ischemic pain with Q waves in the electrocardiogram or T wave inversion with loss of the accompanying r wave, and S–T segment elevation; (2) typical cardiac ischemic pain followed by significant serial elevation of serum enzyme levels (glutamic oxaloacetic transaminase, lactic dehydrogenase, creatine phosphokinase) and S–T or T wave changes in the electrocardiogram; (3) in the absence of typical chest pain, sequential electrocardiographic changes as defined in the first criterion.

Protocol: All patients entering the study received oral doses of quinidine sulfate, 0.4 g, or identical placebo tablets of sodium lactate every 8 hours. Treatment continued for a total of 72 hours or until the patient was withdrawn from the study because of failure to satisfy the cited diagnostic criteria for acute myocardial infarction or because of treatment failure. The drug was routinely administered at 6:00 AM, 2:00 PM and 10:00 PM. Patients admitted within 3 hours after these times were given a full dose of the drug; those admitted between the 3rd and 6th hours received a half dose, and those admitted in the 2 hours preceding the next scheduled dose were given no drug.

During the latter part of the study, 128 blood samples for serum quinidine determinations were drawn from 73 patients between 9:00 and 10:00 AM on the 1st and 3rd days of the study. Analysis was made by the fluorometric method of Brodie and Undenfriend[19] and Edgar and Sokolow[20]; the results were unavailable until completion of the study.

In the coronary care unit a standard 12 lead electrocardiogram was obtained on admission and daily. Each patient's electrocardiogram was continuously displayed on an oscilloscope, and paper records of 10 seconds' duration were obtained at 15 minute intervals. Treatment decisions were based on these observations by the nursing and medical staff of the coronary care unit.

In addition, a continuous electrocardiographic record throughout the entire 72 hours of the study was recorded on magnetic tape at a hospital station that was not geographically part of the coronary unit. These records were made on Phillips FM 7 channel tape recorders, model 400, which were controlled so that a continuous uninterrupted record could be made. These tapes were reviewed independently by two observers, one a trained nurse technician, the other one of the authors. These observers documented arrhythmias appearing on the tapes and specifically noted the number of premature ventricular beats occurring over the 72 hour study period.

Treatment failure: Patients were withdrawn from the study and the appropriate therapy was instituted if failure

of the prophylactic antiarrhythmic treatment was manifested by: (1) the development of ventricular premature beats that were multifocal or had a frequency greater than 5/min, or the occurrence of an R on T phenomenon; (2) ventricular tachycardia or ventricular fibrillation; (3) A–V block greater than first degree; or (4) bundle branch block. Patients were also withdrawn from the study if they manifested shock, acute left ventricular failure or apparent intolerance to the medication.

Of the 246 patients, 103 satisfied the criteria for acute myocardial infarction and were included in the final evaluation. On completion of the study, when the drug code was broken, 58 patients had been receiving placebo and 45 had been receiving quinidine.

The success of the quinidine prophylaxis was evaluated by the following criteria: (1) treatment failure and the arrhythmia responsible for it; (2) quantitation of ventricular premature beats; (3) mortality during the 72 hours of controlled observations; and (4) serum levels of quinidine.

Results

Treatment Failure

The specific arrhythmias resulting in treatment failure are shown in Figure 1. The 38 percent prevalence rate of arrhythmias of all types in the quinidine-treated patients compared with the 50 percent rate in the group receiving placebo suggests a protective effect of quinidine; however, the difference is not statistically significant.

Ventricular tachycardia occurred in 12 of 58 patients treated with placebo and in only 1 of 45 treated with quinidine (chi-squared df2 $P < 0.01$). Ventricular premature beats that were multifocal or had a frequency greater than 5/min resulted in treatment failure in 14 of 58 patients treated with placebo and in only 6 of 45 patients receiving quinidine.

Thus, clinically disturbing ventricular tachyarrhythmias were observed during the first 72 hours in 26 of 58 patients (45 percent) who received the sodium lactate placebo and in only 7 of the 45 patients (16 percent) who received quinidine ($P < 0.05$). Supraventricular arrhythmias were too infrequent to permit a useful comparison. Bradyarrhythmias including heart block were considered serious enough to warrant discontinuance of the trial in 6 of the 45 quinidine-treated patients and in 2 of the 58 patients receiving placebo.

The time at which the occurrence of serious arrhythmia required discontinuance of the trial is shown in Figure 2. The data show an expected predominance of serious arrhythmia early in the first day of the study and reveal no significant differences between the two groups in the time of treatment failure on the first, second or third day.

Quantitation of Ventricular Premature Beats

Twenty-eight patients treated with quinidine and 27 receiving placebo completed the study without serious arrhythmia. The number of ventricular premature beats in each 24 hour period as well as the 72 hour totals were determined (Fig. 3 and 4). Both groups of patients had fewer ventricular premature beats per 24 hour period on successive days.

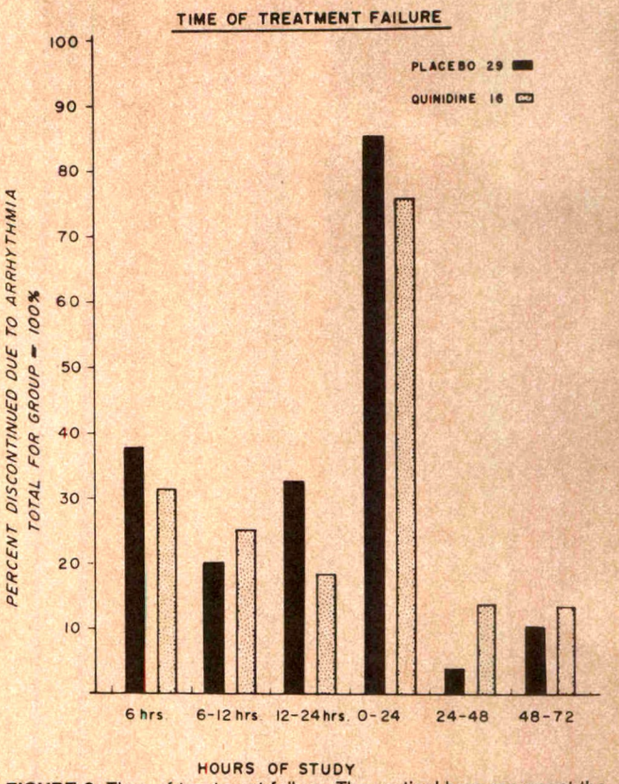

FIGURE 2. Time of treatment failure. The vertical bars represent the percent of patients in each group, placebo- and quinidine-treated, who were withdrawn from the study because of serious arrhythmia during the time intervals shown. Arrhythmias were more frequent in the first 24 hours. There was no systematic difference between the two groups in time of treatment failure.

The greater number of ventricular premature beats in the quinidine-treated patients was largely accounted for by two patients. In one, the number of ventricular premature beats exceeded the sum of ventricular beats for all placebo-treated patients, and in the other almost equaled this sum. Because of the wide scatter of the observations, the difference of the means has no significance. By day 3, 78 percent of the patients receiving placebo and 82.5 percent of those receiving quinidine had fewer than 10 ventricular premature beats per 24 hour period (Fig. 3).

Mortality

The total hospital mortality rate was similar in the two groups: 10.4 percent for patients receiving placebo and 8.9 percent for those receiving quinidine. During the 72 hour study period two patients receiving placebo died of cardiogenic shock. One patient treated with quinidine died within 24 hours. Because this patient first manifested frequent ventricular premature beats, administration of quinidine was discontinued and replaced by treatment with lidocaine. Ventricular fibrillation later occurred and, after successful defibrillation, evidence of bundle branch block noted on the electrocardiogram was followed by a dying heart pattern.

Upon completion of the study and after transfer from the unit, four patients receiving placebo died, two of irreversible cardiac failure and two of sudden cardiac arrest on the 7th and 8th days after infarction. There were three sudden fatal cardiac arrests in the quinidine-treated group, on days 4, 7 and 14 after infarction. Only the patient who died on day 4 had been treated with quinidine for the full 72 hours; the other two had been withdrawn from treatment.

Serum Quinidine Levels

On completion of the study when the results of the serum quinidine concentrations became known, 55 samples containing quinidine had been drawn from 34 patients. The remainder of the 128 serum samples containing no quinidine had been drawn from patients receiving placebo. The 55 serum quinidine samples included some from patients later excluded from the study because infarction was not proved. Individual values are shown in Figure 5.

In nine patients, the initial serum quinidine concentration was below 3 mg/liter. Two of these nine were transferred from the coronary care unit when it was evident they did not have an infarction. Six of the remaining seven patients had a serum level higher than 3 mg/liter when the second sample was taken. Thus only 1 of 32 patients (3.1 percent) did not have a serum quinidine level of 3 mg/liter or higher. Eighty-two percent of samples yielded concentrations in excess of 3 mg/liter; only two samples were above 10 mg/liter.

Side effects: Of the 45 quinidine-treated patients, only 1 was withdrawn from treatment because of nausea and vomiting. Of an additional 77 patients who received quinidine but did not have a proved infarction, 1 was withdrawn from treatment because of nausea and vomiting. A significant prolongation of the Q–T interval was observed in two patients although significant QRS widening was not recorded. No urticarial or other toxic signs were noted.

Discussion

Our study of the efficacy of orally administered quinidine in acute myocardial infarction did not include that significant proportion of patients who die from this condition outside the hospital. Moreover, it did not include those admitted to a coronary unit with "pump" failure, shock or pulmonary edema, or those who obviously required immediate antiarrhythmic treatment with lidocaine, propranolol or other agents. Its focus was on that group of good-risk patients in initially stable condition who would usually be monitored in a coronary care unit for 3 or 4 days and then be transferred to other accommodations if the clinical course was satisfactory. The duration of prophylactic drug administration, 72 hours, was chosen because of the generally acknowledged high frequency of serious arrhythmias within this period. Although one objective was to determine whether sudden death could be prevented, an important second objective was to quantitate the arrhythmias occurring in the treated and control groups by reviewing continuous magnetic tape recordings of the electrocardiogram over the entire 72 hours of observation.

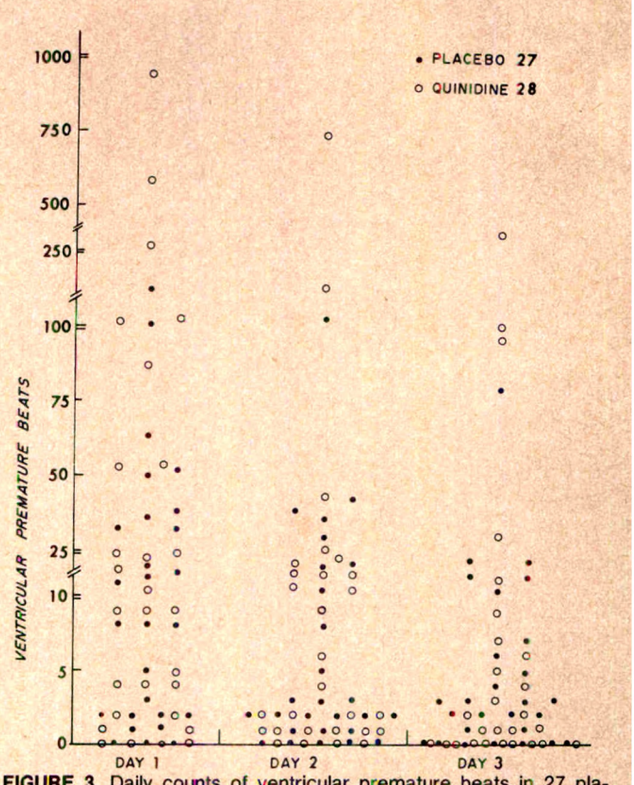

FIGURE 3. Daily counts of ventricular premature beats in 27 placebo-treated and 28 quinidine-treated patients who completed the 72 hour monitoring period without a serious arrhythmia. For each 24 hour period, a closed or open circle marks on the ordinate scale the number of premature beats counted from the magnetic tape record of a single patient.

Effect on survival: The almost identical in-hospital mortality in the two groups indicates that quinidine prophylaxis for 72 hours had no effect on ultimate survival. This is an expected finding since only 3 of the 103 patients died in the first 72 hours. Five patients died suddenly, presumably of ventricular arrhythmia, 4 to 14 days after infarction and after the study period. The occurrence of these late sudden deaths raises the question whether monitoring should be continued for more than the usual 3 to 5 days and suggests that trials of a prophylactic antiarrhythmic regimen should be maintained for 10 to 14 days. Indeed, since our study was conceived, Grace[21] has documented the importance of postcoronary care unit monitoring. Moreover, the Inter-Society Commission for Heart Disease Resources has recommended the inclusion of an intermediate coronary care unit adjacent to or in continuity with the coronary care unit.[22] Such a unit would allow for the management of patients with acute myocardial infarction during the phase of illness when risk of complications, particularly ventricular arrhythmia, has diminished appreciably but not completely.

Effect on prevalence of ventricular tachyarrhythmias: This study has shown that quinidine sulfate administered orally in a dose of 0.4 g every 8

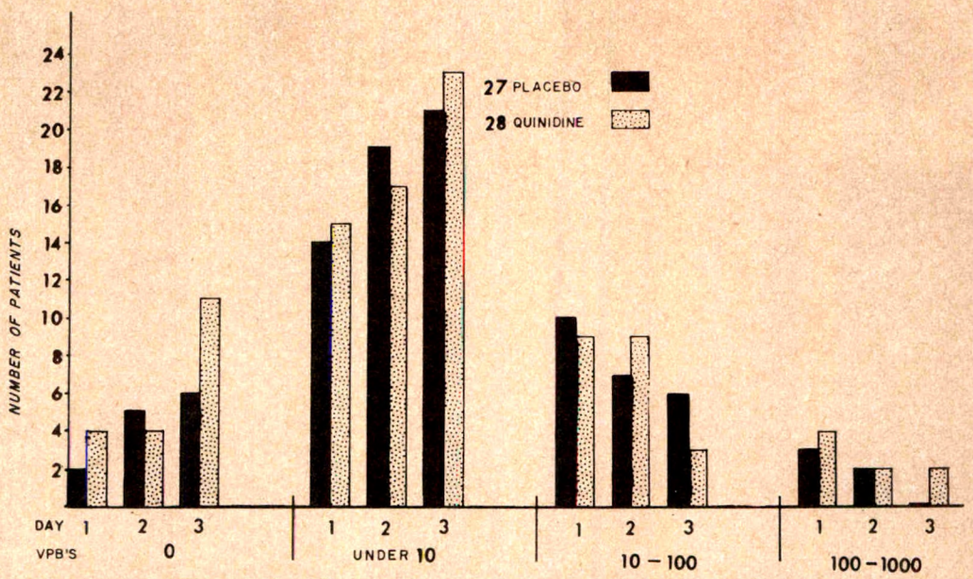

FIGURE 4. Patients who completed 72 hours of monitoring without a serious arrhythmia have been divided for each day of the study into four groups based on the number of isolated ventricular premature beats (VPB's) counted on the 24 hour magnetic tape record. The number of patients with fewer than 10 or no ventricular premature beats increased by the third day; the number with 10 to 100 and 100 to 1,000 decreased by the third day. There is no systematic difference between the quinidine- and placebo-treated groups.

hours will significantly reduce the prevalence of ventricular tachycardia after acute myocardial infarction. It will also significantly reduce the occurrence of ventricular premature beats that are multifocal or have a frequency greater than 5/min. The overall reduction in tachyarrhythmias (from 45 percent in the group receiving placebo to 16 percent in the group receiving quinidine) might be expected to decrease the risk of sudden death if the period of prophylactic therapy were extended beyond 72 hours. The earlier experimental work of de Boer[23] and Wiggers and Wegria[24] and the importance of the R on T phenomenon, first described by Smirk[25] and more recently confirmed in many coronary care unit monitoring programs, strengthen the thesis that both prevention and active treatment of ectopic electrical activity should reduce the risk of sudden death in the early postinfarction period.

Our study affords no encouragement that infrequent isolated ventricular premature beats can be in-

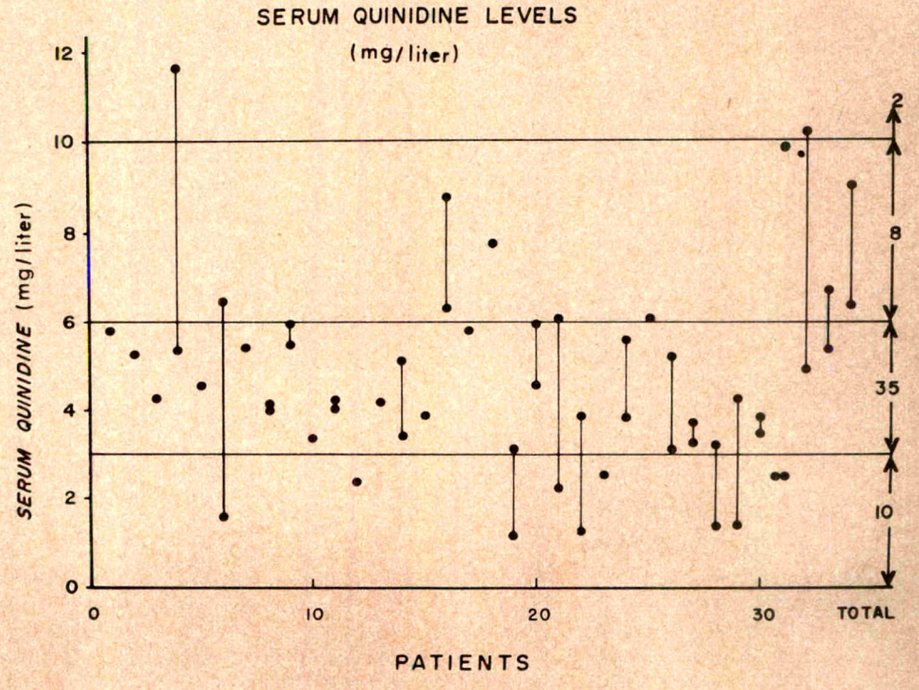

FIGURE 5. Serum quinidine concentrations in 55 samples from patients receiving 0.4 g of quinidine by mouth every 8 hours. **Closed circles** directly superimposed or connected by vertical lines designate the concentration on the first **(bottom)** and third **(top)** days in the same patient.

fluenced by an oral quinidine regimen. There was no significant difference between the groups receiving quinidine and placebo in respect to mean number of isolated ventricular premature beats per 24 hours even when the extremely high values of two quinidine-treated patients were excluded. There was a clear reduction in the total number of ventricular premature beats from the first to the third days but no systematic difference between the two groups. A significant difference was demonstrable when the groups were compared with respect to the number of treatment failures occasioned by the occurrence of ventricular premature beats that were multifocal or had a frequency greater than 5/min.

Serum quinidine levels and cumulation of drug: Some cumulation of quinidine is known to occur during the first 3 days of oral administration,[26] and in many of our patients, serum quinidine levels were higher on the third than on the first day. If the higher levels achieved later in the treatment period were of critical therapeutic significance, it would be expected that the protective effect of quinidine would be more evident at these later times. The data displayed in Figure 2 indicate that there was no systematic difference between the placebo- and quinidine-treated groups in respect to time of treatment failure manifested by a serious arrhythmia. Cumulation of the drug over the 72 hour period, therefore, did not appear to influence the results. On oral regimens of quinidine maximal serum concentration is achieved in 1 to 3 hours after ingestion and is relatively well maintained for 6 to 8 hours, with some cumulation in the first 12 hours but not thereafter.

The reduction in frequency of tachyarrhythmias due to quinidine was at the expense of a modest increase in bradyarrhythmias and A–V dissociation. Two patients were categorized as treatment failures for what could be considered side effects of quinidine. The first had atrial tachycardia with varying block with bradycardia and serum quinidine concentrations of 6.0 and 7.6 mg/liter. The second had serum quinidine levels of 2.1 rising to 6.0 mg/liter on the third day before treatment was discontinued because of nodal bradycardia (rate 40/min).

Acknowledgment

We are indebted to the late Mr. G. Steward, Technical Director, Cardiovascular Unit, Victoria Hospital, who designed and supervised the mechanism for the remote recording of the 72 hour tapes on these patients. We are also indebted to Ms. G. Aggersbury, RN, and Ms. A. Thompson, RN, who reviewed the tapes and assisted in compiling the data.

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Comprehensive Treatment Plan for the Prevention of Primary Ventricular Fibrillation in Acute Myocardial Infarction

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This report of 1,165 cases of acute myocardial infarction outlines a method for preventing primary ventricular fibrillation in patients with this lesion. The plan of prevention begins in the emergency room, with every patient suspected of having myocardial infarction receiving an intravenous bolus injection of lidocaine, 75 mg, followed by a 2 mg/min infusion controlled by an infusion pump. If administration of lidocaine is ineffective (19 percent of cases), procainamide is given intravenously in a dose of 100 mg every 5 minutes, repeated as necessary to a maximum of 1 g and followed by an infusion of 2 to 6 mg/min. Ventricular tachycardia is rapidly converted to sinus rhythm by either drug or electrical therapy. Monitoring by telemetry is continued after the patient's discharge from the coronary care unit. A new episode of sustained chest pain requires the reinstitution of prophylactic lidocaine therapy.

Important precautions to control the toxic effects of these intravenous medications can be achieved in the community hospital where the nursing staff makes the decision to increase the dose of lidocaine or to substitute procainamide. There has been no recognized mortality from the use of these drugs as outlined. With this total system of care, the prevalence rate of primary ventricular fibrillation has been decreased from 6.5 percent (9 of 139 cases) to 0.3 percent (3 of 1,026 cases) and no deaths have occurred.

Prevention and treatment of primary ventricular fibrillation during the course of an acute myocardial infarction are the most important functions of the coronary care unit. Despite the reduced incidence of this type of cardiac arrest since the advent of such units, continued reports emphasize both the occurrence and associated mortality of primary ventricular fibrillation.[1–8]

These studies have raised the following questions: (1) Is primary ventricular fibrillation always preceded by "premonitory" arrhythmias? (2) Once premonitory arrhythmias occur, is there sufficient time for the institution of drug therapy to prevent primary ventricular fibrillation? (3) Are the currently used drugs effective in suppressing these premonitory arrhythmias or preventing primary ventricular fibrillation?

The purpose of this report is to answer these questions and describe a method for preventing primary ventricular fibrillation. The technique has been developed over the past 7 years in a community hospital with neither a full time unit director nor house staff. This plan of treatment has reduced the prevalence rate of primary ventricular fibrillation from 6.5 percent (9 of 139 cases) to 0.3 percent (3 of 1,026 cases).

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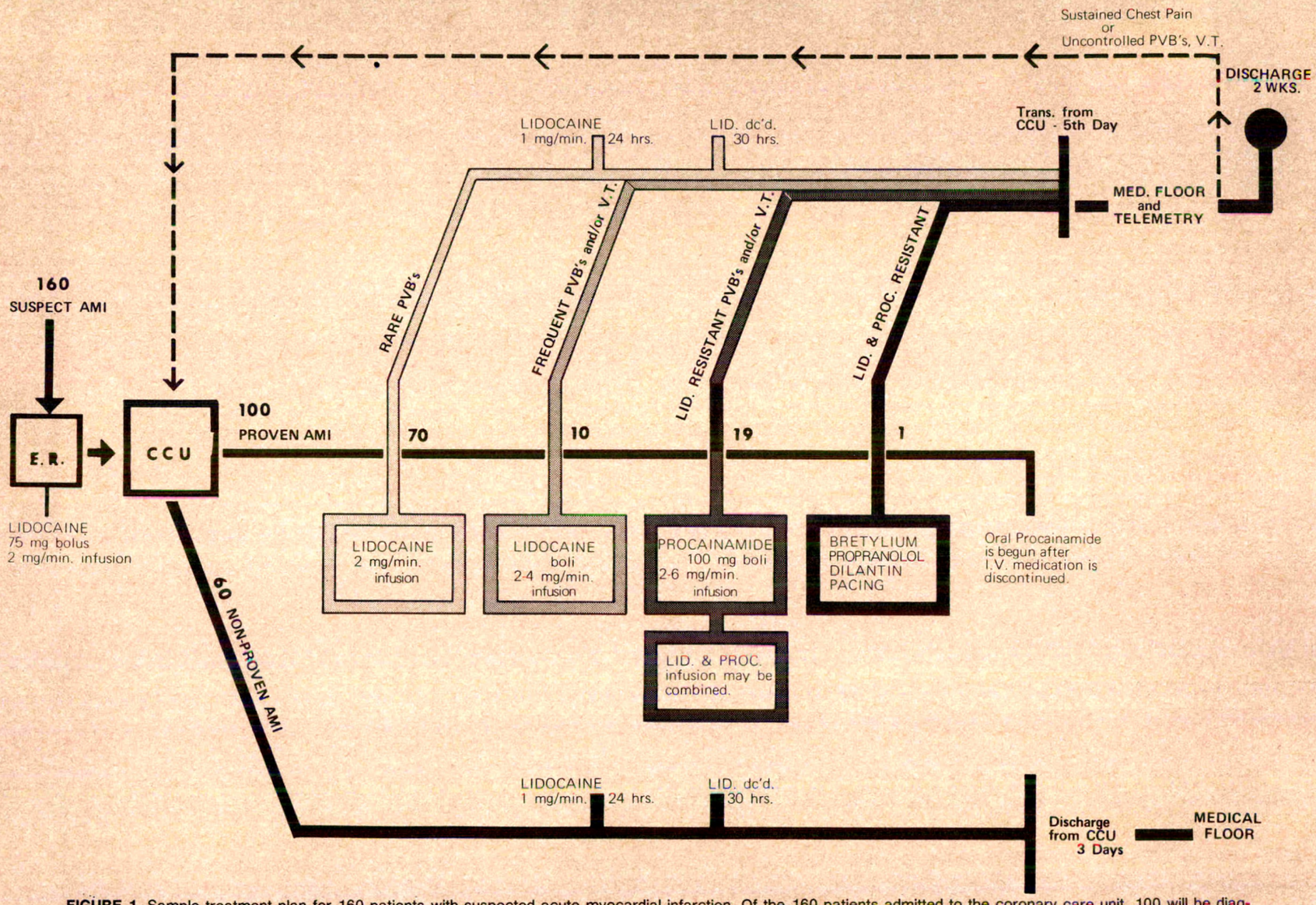

FIGURE 1. Sample treatment plan for 160 patients with suspected acute myocardial infarction. Of the 160 patients admitted to the coronary care unit, 100 will be diagnosed as having had an acute myocardial infarction. The plan represents treatment given to the last 611 patients with proved infarction. AMI = acute myocardial infarction; boli = bolus injection; CCU = coronary care unit; E.R. = emergency room; I.V. = intravenous; LID. = lidocaine; MED. = medical; PROC = procainamide; PVB's = premature ventricular beats; VT = ventricular tachycardia.

Methods

The data were collected during a 7 year period in a 165 bed community hospital that has neither house staff nor a full time unit director. All patients (1,165) diagnosed as having an acute myocardial infarction since the inception of the unit in 1966 were included in the study. The criteria for the diagnosis of acute myocardial infarction have been previously described[9] and were the same as those used for the diagnosis of myocardial infarction in the California Regional Medical Program Study. Analysis of the electrocardiograms revealed new or significant change in preexisting Q waves in 78 percent of cases and evolutionary S–T and T wave changes without Q waves in 22 percent. All patients had significant rises in serum enzyme levels with at least a 100 percent increase in serum glutamic oxaloacetic transaminase and creatine phosphokinase. In this series 23 percent of all deaths occurred in the group without Q waves.

Primary ventricular fibrillation was defined as fibrillation occurring in the absence of pulmonary edema or shock. All cases of secondary fibrillation occurred as an agonal event or when the patient had profound shock or pulmonary edema. Only cases of primary ventricular fibrillation occurring in the coronary care unit were included. The average duration of stay in the unit was 4.5 days.

Arrhythmias were documented in the coronary care unit with standard monitoring equipment utilizing an alarm-triggered electrocardiogram, a memory loop and, in selected cases, a 10 hour continuous tape. Both lidocaine and procainamide were administered to patients by the nurse, as directed by a set of standing orders. Ventricular tachycardia was immediately terminated electrically (direct-current capacitor discharge) by the nurse if clinical deterioration occurred. Serum potassium determinations were performed in all patients on admission to the unit, and potassium replacement was begun immediately if hypokalemia existed.

Treatment Plan

In Group I (the first 139 patients with confirmed acute myocardial infarction), prophylactic treatment was limited to orally administered procainamide or quinidine when multiple premature ventricular beats were observed. The doses were 250 or 500 mg of procainamide or 200 or 400 mg of quinidine every 4 to 6 hours, as determined by the attending physician. Ventricular tachycardia was treated with an intravenous infusion of procainamide at a rate of 50 to 100 mg/min until the arrhythmia was abolished or 1 gram of procainamide had been given. Electrical conversion was used if clinical deterioration was evident or if the use of procainamide had been unsuccessful.

In Group II, (the last 1,026 patients with confirmed acute myocardial infarction), prophylactic intravenous administration of lidocaine was begun, and, if unsuccessful, procainamide was given intravenously. In the first subgroup (IIA, 145 patients) the criteria for initiating a lidocaine drip infusion were as follows if premature ventricular beats: (1) occurred on the T wave, (2) occurred in bursts (two in succession), (3) were multifocal, or (4) exceeded a rate of 5/min. In the second subgroup (IIB, 270 patients) prophylactic administration of lidocaine was begun when the first premature ventricular beat was observed. The third subgroup (IIC, 611 patients) reflects the current procedure of administering lidocaine to every patient with suspected myocardial infarction.

The treatment plan for every patient with suspected myocardial infarction begins in the emergency room. The doses of lidocaine, and procainamide if needed, are as follows: Lidocaine, 50 mg, is given intravenously as a bolus injection, followed by 25 mg over the next minute. A 2 mg/min drip infusion is then begun and continued over the next 24 hours. It is then slowly diminished and discontinued over the next 6 hours if no premature ventricular beats are observed. The patient is then given procainamide, 250 mg orally, every 4 hours until discharge from the hospital. If the premature ventricular beats are not controlled by the 2 mg/min infusion of lidocaine, a second and, if necessary, a third bolus injection of lidocaine is given, and the infusion rate is increased to a maximum of 4 mg/min. If lidocaine is ineffective at this dose, intravenous administration of procainamide is started. An infusion of 100 mg is given every 5 minutes and repeated as necessary (not to exceed 1 gram) to suppress ventricular extrasystoles. This is followed by infusion at a rate of 2 mg/min, which may be increased to 6 mg/min. The two drugs given in combination have appeared at times to have a more suppressant effect than either alone. If ventricular tachycardia ensues (rates over 100/min) and is sustained despite drug treatment, electrical conversion is immediately carried out.

After the patient is discharged from the coronary care unit to the ward, an intravenous pathway is maintained for 48 hours. Monitoring by telemetry is continued during the convalescent period. A patient experiencing a new episode of sustained chest pain during the convalescent period again receives prophylactic intravenous infusions of lidocaine. A flow chart of the entire treatment plan is shown in Figure 1.

The dose of lidocaine or procainamide is halved if shock, serious congestive failure or renal failure is present, since lidocaine is primarily detoxified by the liver and procainamide by the kidney.[10,11] Blood pressure and QRS duration are carefully monitored when procainamide is given. Administration of this drug is withheld in the presence of second or third degree atrioventricular (A–V) block if a pacing catheter has not been inserted. If muscular twitching or change in sensorium is noted during the administration of lidocaine, the dose is decreased. Premature or escape ventricular beats resulting from sinus bradycardia or bradycardia due to heart block require increasing the ventricular rate by administration of atropine or cardiac pacing. If the ectopic beats continue after the ventricular rate is increased, suppressant therapy will be given as previously outlined.

The following rules have been developed to prevent lidocaine toxicity:

1. All patients receive lidocaine by infusion pump.
2. Lidocaine is not given at a rate higher than 4 mg/min.
3. The dose of lidocaine is halved in the presence of severe congestive failure or shock.
4. In uncontrolled atrial arrhythmias, the ventricular rate is slowed before treatment with lidocaine is begun.[12,13]
5. If ectopic ventricular beats appear to be enhanced by lidocaine (a rare occurrence), intravenous infusion of procainamide is substituted.

Results

Prevalence and clinical factors: The mortality rate for the total series of 1,165 patients with acute myocardial infarction was 10.2 percent. The mean age of all patients in the series was 63 years. Shock occurred in 10 percent, and moderate or severe congestive failure in 25 percent. Time from onset of pain until hospital admission was calculated in each case.

TABLE I

Prevalence of Primary Ventricular Fibrillation Before and After Use of Prophylactic Intravenous Administration of Lidocaine or Procainamide

	Patients with Proved AMI (no.)	Criteria for Prophylaxis	Prophylaxis Plan	Primary VF (no. of cases)	Primary VF (%)
Group I	139	Multiple PVBs	Procainamide or quinidine (orally)	9	6.5
Group II	1,026	...	Lidocaine (intravenous bolus	3	0.3
A	145	"Standard" criteria	injection, then infusion to 4	0	...
B	270	1st PVB	mg/min); if unsuccessful,	1	...
C	611	On admission with suspected AMI	procainamide (intravenous bolus injection, then infusion to 6 mg/min)	2	...

AMI = acute myocardial infarction; PVB = premature ventricular beat; VF = ventricular fibrillation.

Fifty-eight percent of patients were admitted within 4 hours of onset and 29 percent within 1 hour of onset. Pump failure was the cause of death in all cases except for one case of primary ventricular fibrillation. Primary ventricular fibrillation occurred in 12 patients in the entire series; 1 of the 12 died despite immediate defibrillation. The other 11 were discharged from the hospital and are alive 6 to 84 months after the event. Table I shows the prevalence of primary ventricular fibrillation before and after prophylactic use of lidocaine and, if necessary, procainamide. Before this procedure was adopted, the prevalence rate of primary ventricular fibrillation was 6.5 percent (9 of 139). After its adoption, primary ventricular fibrillation occurred 3 times in 1,026 cases (0.3 percent).

Premonitory cardiac arrhythmias: Table II shows the characteristics of the 12 patients with ven-

TABLE II

Characteristics of Patients with Primary Ventricular Fibrillation

Case no.	Age (yr) & Sex	Time (hours) From Pain to Admission	Time (hours) From Admission to Fibrillation	Time (hours) From Pain to Fibrillation	Site of Infarct	Premonitory Rhythm	Prophylactic Medication	Outcome
1	44M	1	1	2	Inf	Sinus with PVBs	None	A
2	45M	1	2	3	Inf	Sinus tachycardia with PVBs	None	A
3	53M	1	2 1/2	3 1/2	Inf	Sinus with PVBs	Lidocaine (3 mg/min)	A
4	54F	1	1	2	Inf	Sinus with PVBs	Quinidine	A
5	56M	1	15	16	Inf	Atrial flutter with rare PVB	Digitalis; none	D
6	58M	1	3	4	Ant	Sinus with no PVBs	None	A
7	60M	3	137	140	Inf	Atrial flutter with rare PVB	Procainamide (orally); lidocaine (intravenously, 2 mg/min)	A
8	63M	2	10	12	Inf	Sinus with rare PVB	None	A
9	63M	12	20	32	Ant	Junctional with rare PVB	Quinidine	A
10	69M	12	1/3	12	Ant	Sinus with rare PVB (R on T)	None	A
11	71F	3	2	5	Ant	Sinus with rare PVB (R on T)	Quinidine	A
12	77F	6	3	9	Inf	Junctional with PVBs	None	A

A = alive; Ant = anterior; D = died; Inf = inferior; PVB = premature ventricular beat.

tricular fibrillation. More than half (7 of 12) were 60 years of age or less; the average age was 59. In 8 of the 12, ventricular fibrillation developed within 3 hours of the patient's admission to the coronary care unit; in 6 of the 12, it occurred within 5 hours of the onset of pain. In seven, only a rare or no premature ventricular beat was noted before the onset of the fibrillation. No episode of primary ventricular fibrillation was immediately preceded by ventricular tachycardia or preceded at any time by sinus bradycardia, junctional bradycardia or A–V block. Two episodes occurred after inadequate control of atrial flutter. The single death from primary ventricular fibrillation occurred before the use of lidocaine. This patient had atrial flutter with a ventricular rate of 150/min. Digoxin was given intravenously, but shortly thereafter, with only a rare ectopic ventricular beat, ventricular fibrillation occurred. Defibrillation was unsuccessful.

In one patient (Group IIB) with primary ventricular fibrillation there were no preceding ectopic ventricular beats, as documented with use of a 20 minute memory loop. This occurrence of primary ventricular fibrillation without any warning prompted the initiation of prophylactic lidocaine therapy to all patients with suspected myocardial infarction (Group IIC). One patient in this latter group had ventricular fibrillation on the fifth hospital day. His course was complicated by hypotension, heart failure, multiple pulmonary emboli and atrial fibrillation and flutter. Despite intravenous administration of digitalis, the ventricular rate was not adequately slowed, and during one of many episodes of atrial flutter, ventricular fibrillation ensued, which was converted to sinus rhythm by direct-current defibrillation. At the time of the ventricular fibrillation, the patient was receiving a 2 mg/min infusion of lidocaine. The second patient in Group IIC who demonstrated ventricular fibrillation was given a 3 mg/min infusion of lidocaine after a brief run of bigeminy. No ectopic ventricular beats were noted for 15 minutes before the occurrence of ventricular fibrillation.

Treatment outside the coronary care unit: The prevalence data on primary ventricular fibrillation in this report have included only those documented cases occurring in the coronary care unit. The treatment program during the 7 years was expanded to include the emergency room area and the general medical floor. In those patients who received lidocaine therapy in the emergency room (last 611 cases), no cases of primary ventricular fibrillation occurred either in the emergency room, on the elevator or in the halls as the patient was transported to the unit. Three cases of primary ventricular fibrillation occurred in the emergency room before intravenous tubing could be inserted and lidocaine administered.

Monitoring after discharge from the unit was used in the last 810 cases. Sudden death has rarely occurred since the addition of this step to the program. Five patients died suddenly on the medical floor, but the arrhythmia at the precise moment of clinical death was not recorded since the telemetric equipment has no memory loop. Two of these patients underwent autopsy; one had a large fresh pulmonary embolus in the left main pulmonary artery, and one a fresh occlusion of the left main coronary artery.

Other treatment for ventricular arrhythmias: It was necessary to supplement or replace lidocaine with procainamide in 19 percent of patients because of inadequate control of the ectopic ventricular rhythms. In less than 1 percent of patients requiring procainamide, the ventricular rhythm still could not be controlled. Diphenylhydantoin, bretylium tosylate, propranolol hydrochloride or overdrive pacing was then used. Rapid ventricular tachycardia was quickly and successfully converted to sinus rhythm by chemical or electrical therapy.

Accelerated idioventricular rhythm was generally controlled by administration of atropine. However, a gradual acceleration of the focus was commonly observed and, in these instances, lidocaine or procainamide proved effective. In two patients with an accelerated idioventricular rhythm, a 2:1 exit block was recognized when the ventricular rate exceeded 160/min. It should be pointed out that most ectopic ventricular rhythms occur in the first 24 hours of an acute myocardial infarction; in some instances, it is difficult to determine if time alone is as important as drug therapy in controlling the ventricular rhythms. In others, a prior history of ventricular premature beats is associated with difficulty in suppressing such a focus.

Lidocaine and Procainamide Toxicity

Lidocaine: This agent has been used in more than 1,550 patients since the inception of the coronary care unit. Infarction was documented in approximately 950 patients; more than 550 patients were found to have had no infarction. The latter patients experienced no significant side effects from the administration of lidocaine (75 mg bolus injection and a 2 mg/min drip infusion). Minor transient central nervous system complaints could be elicited after the initial bolus injection; spontaneous complaints were unusual. In the patients with documented myocardial infarction, effects on the central nervous system were dose-related. Three patients early in the series had convulsions caused by a "runaway" infusion. This complication has since been prevented by the use of infusion pumps in all patients. No adverse hemodynamic effects were found.

The effects of lidocaine on the sinus rate and P–R, QRS and Q–T durations were studied in 100 consecutive patients. These measurements were performed on the surface electrocardiogram every minute for the first 15 minutes after the initial 75 mg bolus injection, and then hourly for the ensuing 30 hours. No statistically significant effects were found. Twenty patients in this group had sinus rates of less than 60/min, and none manifested further slowing. Blood lidocaine levels were serially measured in 25 patients who had received the bolus injection plus the 2 mg/

min infusion. The results showed that no patient demonstrated drug buildup after administration of lidocaine for a 30 hour period.

Procainamide: Intravenously administered procainamide was used in 19 percent of patients because of the ineffectiveness of lidocaine. With this method of administration, serum procainamide levels did not exceed 10 mg/liter. Significant widening of the QRS duration was recognized in one case, and prolongation of the Q–T interval was frequently observed. Significant hypotension rarely occurred.

Discussion

As currently used throughout the world, lidocaine prophylaxis has reduced the mortality from acute myocardial infarction, but many patients still experience primary ventricular fibrillation and subsequently die. In many cases these deaths occur because the so-called premonitory ventricular rhythms are absent or unrecognized.[14] Bennett and Pentecost[8] clearly documented the absence of electrocardiographic warning in 27 patients with primary ventricular fibrillation: Five (19 percent) had no warning at all, 2 (7 percent) had warning for less than 5 minutes, and 20 (74 percent) had fewer than five premature ventricular beats per minute. In our study, 7 of 12 patients with primary ventricular fibrillation had no premonitory ventricular arrhythmias. In other studies[3–8] from 25 to 83 percent of such patients have had no warning arrhythmia.

Factors in prevalence of ventricular fibrillation: Prevalence data on primary ventricular fibrillation have been documented in only a few reports and have generally been limited to instances in the coronary care unit. The rates have ranged from 2.4 to 10 percent. Data on the prevalence of primary ventricular fibrillation in the emergency room and after discharge from the coronary care unit are sorely needed. Because most of the published reports are from units with both house staff and full time director and data from large numbers of community hospitals are lacking, it is not possible to estimate the true incidence of this potentially lethal complication. In a recent 3 year study[15]•conducted in 100 hospitals in California, the prevalence rate of primary ventricular fibrillation in the coronary care unit was 5 percent (793 of 15,031 cases), and 47 percent of these patients died. Of all the deaths that occurred in the entire study, 17 percent were due to a primary arrhythmia.

Two major factors other than treatment may account for differences in the prevalence rate of primary ventricular fibrillation from one hospital to another. The first is definition of the arrhythmia; the second, the rapidity with which patients are hospitalized.

Definition: The definition of primary ventricular fibrillation used in our study is more inclusive than that generally used.[16,17] In our hospital patients who have ventricular fibrillation accompanied by moderate congestive failure are classified as having primary fibrillation; only patients with pulmonary edema or shock are considered to have secondary ventricular fibrillation.

Time from onset of symptoms: The second factor that may influence the prevalence rate of primary ventricular fibrillation is the interval between onset of symptoms and hospitalization. In our study 58 percent of patients were hospitalized within 4 hours and 29 percent within 1 hour; this delay is generally less than that reported in other studies.[3–6,18,19]

Effect of treatment plan: Neither of the preceding factors accounts for the low prevalence rate reported here. Since our definition of primary ventricular fibrillation was more inclusive and our patients were hospitalized earlier during their acute myocardial infarction than in other reported series, the extremely low prevalence rate (0.3 percent) of primary ventricular fibrillation in our study must have resulted from the treatment plan.

This plan takes into account the multiple conditions that predispose the patient to primary ventricular fibrillation and deals with each in a specific manner. The high prevalence rate during the first hours and the lack of warning arrhythmias are countered by the use of lidocaine in every case of suspected myocardial infarction in the emergency room. There is evidence that lidocaine has a direct effect on the myocardium, decreasing its vulnerability to development of fibrillation.[20] The ineffectiveness of lidocaine in approximately 19 percent of patients is dealt with by the early use of intravenously administered procainamide. The danger of a rapid ventricular tachycardia degenerating into ventricular fibrillation is countered by rapid conversion to sinus rhythm by chemical or electrical means. The high rate of sudden death after a patient is transferred from the coronary care unit is prevented by telemetric monitoring until time of discharge, and reinstitution of prophylactic lidocaine therapy if a new episode of chest pain occurs or new bursts of ectopic ventricular beats are recognized.

Reports of controlled trials with routine antiarrhythmic prophylaxis have shown a reduction in ectopic ventricular rhythms but not in primary ventricular fibrillation; this finding is expected.[21–23] The control patients in all of the reported studies were given lidocaine as soon as premonitory ventricular arrhythmias were recognized and were therefore removed from the control population. In addition, the number of cases in each trial was small. A controlled trial of a plan involving multiple steps, such as that presented here, would be a difficult undertaking in a single hospital. A cooperative study involving several institutions may be able to test this treatment program. We believe that primary ventricular fibrillation is a preventable complication of acute myocardial infarction, requiring a plan that recognizes the precise time the patient is most susceptible and, in the absence of the physician, the initiation of prophylactic measures by nursing personnel.

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Ostium Secundum Atrial Septal Defect Associated with Balloon Mitral Valve in Children

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Eight children with an ostium secundum atrial septal defect and balloon mitral valve are described. Leftward-superior QRS forces, abnormal T waves and suggestive apical auscultatory findings (midsystolic click or a late systolic murmur of mitral insufficiency) were frequently observed and led to the erroneous diagnosis of ostium primum atrial septal defect in six cases. Lack of any or all of these manifestations did not preclude the presence of a balloon mitral valve. The prognostic importance of this valvular lesion indicates the need to perform left ventriculography in all patients with an atrial septal defect.

Balloon mitral valve, also termed prolapsing or billowing mitral valve, is an anomaly characterized by aneurysmal protrusion of the posterior or anterior mitral valve leaflet, or both, into the left atrium, usually late during ventricular contraction. This lesion has been the subject of several reviews of data in large numbers of cases.[1–4] Although patients with an associated ostium secundum atrial septal defect have occasionally been included in the reported series,[5–9] the direct association of these lesions has only recently been reported.[10,11]

In this paper we emphasize the association of balloon mitral valve with ostium secundum atrial septal defect and report the clinical and laboratory findings in a series of eight children. Our observations indicate that a balloon mitral valve should be suspected in all children with an ostium secundum atrial septal defect, especially those who demonstrate unusual electrovectorcardiographic features or suggestive auscultatory findings. Identification of the lesion is important since these patients may be thought to have an ostium primum atrial septal defect (partial form of endocardial cushion defect) or may experience significant complications such as mitral valve insufficiency, potentially dangerous cardiac dysrhythmias or infective endocarditis.

Material and Methods

All eight patients were evaluated at the University of Florida Medical Center. Their ages ranged from 3 to 14 years; two were female. None had a history of rheumatic fever or showed signs of Marfan's syndrome. Complete studies including chest roentgenograms (four views with barium), phonocardiograms, 14 lead electrocardiograms and Grishman cube vectorcardiograms were obtained in all. Right and left cardiac catheterization with selective left ventriculography was performed in every patient.

Results

Clinical findings (Table I): Half of the patients were symptomatic, demonstrating decreased exercise tolerance. One patient had Noonan's syndrome (hypertelorism with Turner phenotype and normal chromosomes[12]), and three had evidence of mental retardation. All had clinical and X-ray findings compatible with an atrial septal defect. Three patients had an apical midsystolic click; one of these and another patient also had a murmur of mitral insufficiency.

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TABLE I

Clinical and Electrocardiographic Findings

Case no.	Age (yr) & Sex	Apical Click	MI Murmur	Mean Frontal QRS Axis	ECG Diagnosis	T in V_6	Surgery	Associated Defects
1	3M	No	No	−30°	Normal	+	No	Mental retardation; seizures
2	3M	Yes	No	−60°	RVH	+	Yes	Functional speech defect; tricuspid valve insufficiency
3	7M	No	No	+150°	RVH	+	Yes	None
4	10M	No	Yes	+170°	RVH	−	Yes	None
5	11M	Yes	No	+130°	RVH	−	No	Noonan's syndrome
6	12F	No	No	+190°	RVH	+	Yes	Partial anomalous pulmonary venous return; pulmonic stenosis; mental retardation; congenital nystagmus
7	13M	Yes	Yes	Indeterminate	BVH	+	Yes	None
8	14F	No	No	+180°	WPW RBBB	+	Yes	Mental retardation

+ = positive; − = negative.

BVH = biventricular hypertrophy; MI = mitral valve insufficiency; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; WPW = Wolff-Parkinson-White syndrome.

Electrocardiographic and vectorcardiographic findings (Table I): Two patients demonstrated premature supraventricular beats. Five patients had right axis deviation, two left axis deviation (Fig. 1) and one an indeterminate axis. Five patients manifested right ventricular hypertrophy, one had a normal tracing and the one patient with significant mitral insufficiency (Case 7) had biventricular hypertrophy. Patient 8 presented with Wolff-Parkinson-White syndrome and right bundle branch block. Two patients had negative T waves in lead V_6.

The majority of the frontal QRS loops were unusual for ostium secundum atrial septal defect (Fig. 2). Four patients (Cases 1, 2, 3 and 7) had a leftward QRS loop with counterclockwise or complex inscription. In four the loop had a clockwise inscription, but in three of these patients (Cases 4, 6 and 8) large rightward and superior terminal QRS forces were observed.

In six patients the diagnosis of an ostium primum atrial septal defect (endocardial cushion defect type) was made at the first clinical evaluation primarily on the basis of the electrocardiogram or vectorcardiogram, or both. In two patients (Cases 2 and 6) the erroneous diagnosis had been made previously after cardiac catheterization at another medical center.

Cardiac catheterization: The presence of a left to right shunt at the atrial level was demonstrated by

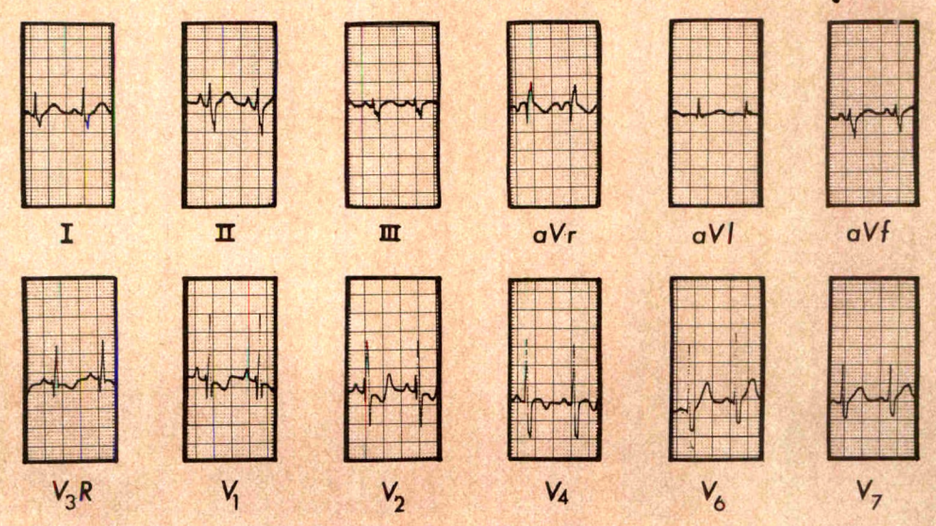

FIGURE 1. Case 2. Electrocardiogram revealing left axis deviation, right atrial enlargement and right ventricular hypertrophy.

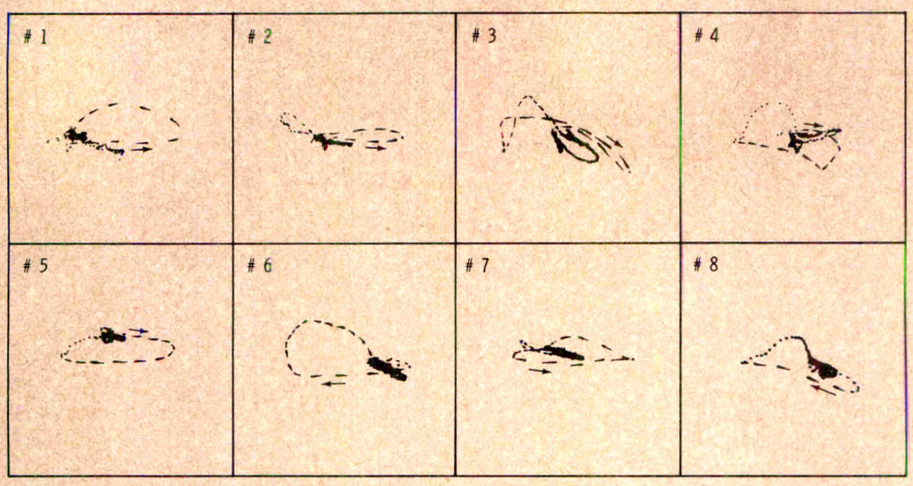

FIGURE 2. Frontal plane Grishman cube vectorcardiograms in eight cases. Cases 1, 2, 3 and 7 have leftward QRS loops with counterclockwise or complex inscription, similar to those observed in association with ostium primum atrial septal defects.

cardiac catheterization data in all patients. The pulmonary to systemic flow ratio (Qp/Qs) ranged from 1.3:1 to 5.5:1. Right ventricular peak systolic pressures were normal except in Patient 6, who had associated pulmonic stenosis.

Left ventriculography: Biplane seriographic anteroposterior and lateral view left ventriculography was performed in six patients and single plane left cineventriculography in the right anterior oblique projection in two. In each patient there was evidence of a ballooning or prolapsing mitral valve leaflet. The posterior or mural leaflet was involved in all eight cases; in four, the anterior (septal) leaflet was also deformed.

In the biplane studies the prolapsing mitral valve produced a distinct pattern in all six patients. In the anteroposterior projection, as contrast medium collected in the prolapsing component of the posterior leaflet, a sausage-like density appeared superimposed over the superior component of the medial and lateral walls of the outflow tract (Fig. 3A and 4B). In one patient with mitral valve incompetence this configuration was less apparent. In two patients who were rotated to a slightly right oblique position, the prolapsing leaflet projected as a discrete aneurysmal bulge along the medial aspect of the left ventricular outflow tract. This appearance is important since it can be confused with an aneurysm of the membranous portion of the ventricular septum. In the lateral view the prolapsing valve appeared as cauliflower-like projections directed posteriorly, seen best in systole (Fig. 3B).

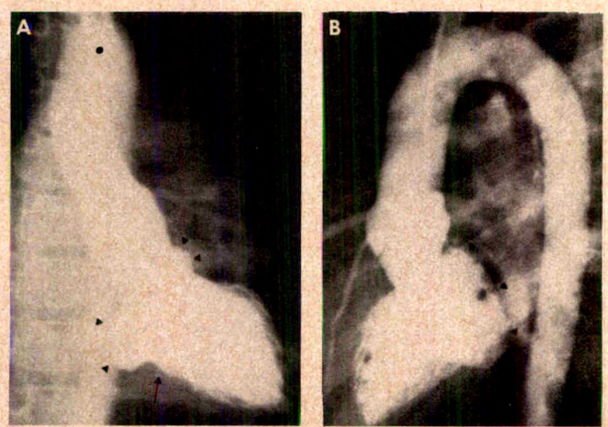

FIGURE 3. Case 6. Selective left ventriculograms (end-systolic films). **A,** anteroposterior view; **B,** lateral view. In **A,** the prolapsing mitral valve projects on both sides of the left ventricular outflow tract **(triangles).** There is a posteroinferior wall deformity **(arrow)** and an area of asynergism along the superior wall. In **B,** the triangles point toward the prolapsing valve.

The two patients undergoing right anterior oblique left cineventriculography also showed prolapse of the mitral valve into the left atrium. Of these, one had mitral valve incompetence.

Analysis of the motion of the left ventricle revealed that, although contractions were vigorous, three of eight patients had asynergistic contractions or relaxations; in each this was shown by an anterior convex bulging in the mid-aspect of the anterolateral wall in systole (Fig. 4A). In addition, one patient had a localized systolic indentation of the inferoposterior wall into the left ventricular cavity (Fig. 3A), and one patient demonstrated apical akinesia.

Of the two patients with mitral valve incompetence, one manifested the asynergistic abnormality of the anterolateral wall; in the other the ventricle contracted normally. We believe that analysis of ventricular motion in relation to asynergism is best accomplished by right anterior oblique cineventriculography rather than by seriography in the anteroposterior and lateral projections.

Surgical findings and treatment: Surgical closure of the ostium secundum atrial septal defect was accomplished in six patients. Two patients required a patch, Patient 4 because the defect was large and Patient 6 because of anomalous connection of the right pulmonary veins to the right atrium.

The mitral valve was examined in five patients: Two had no significant abnormality, but three had obvious changes. Patient 4 had a large prolapsing

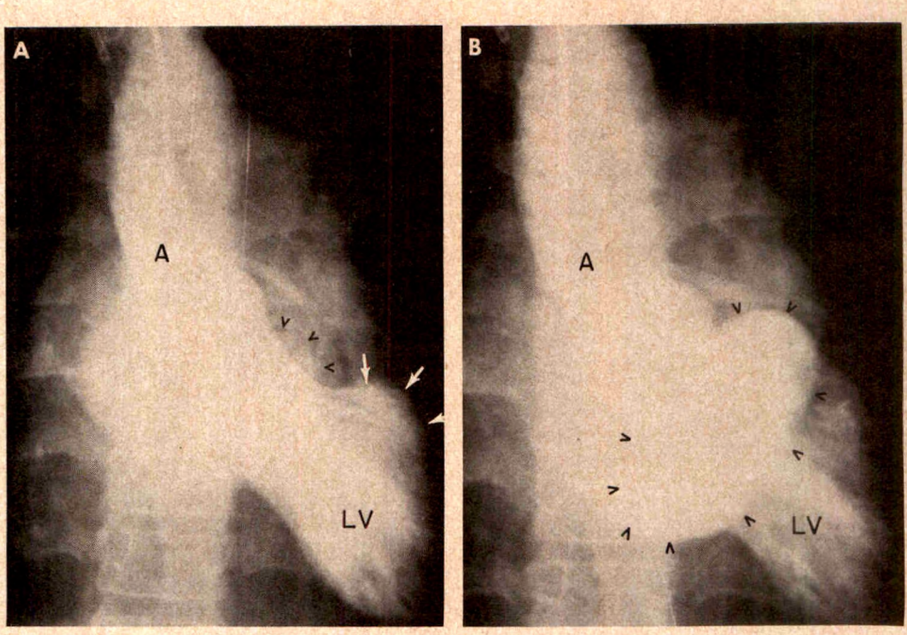

FIGURE 4. Case 7. Anteroposterior selective left ventriculograms. In **A**, mitral valve prolapse is seen on both sides of the left ventricular outflow tract, especially the lateral side (V). Because of mitral valve insufficiency, prolapse seen medially is less apparent because it is superimposed over contrast material in the left atrium. The **arrows** indicate the systolic bulge along the anterolateral wall of the left ventricle (LV). In **B**, the prolapsing mitral valve is more apparent in late systole and appears as a sausage-like mass (V).

posterior leaflet and Patient 6 a redundant anterior leaflet; in Patient 7 the mitral valve had a myxomatous appearance with thickened and prolapsed anterior and posterior leaflets. No cleft of the anterior leaflet was observed in any instance and nothing was done to the malformed valves. Patient 6 also underwent pulmonary valvotomy.

Postoperative cardiac rhythm disturbances were documented in every case. In two patients, right ventricular conduction delay developed. Two patients had temporary nodal rhythm, which in one was associated with complete right bundle branch block. Patients 4 and 8 had episodes of supraventricular tachycardia with variable second degree atrioventricular conduction.

Cardiac auscultation after operation revealed persistence of the murmur of mitral insufficiency in Patients 4 and 7. In the other patients, the apical click became apparent or more distinct. Postoperative cardiac catheterization studies were performed in two patients. In Case 2 the study disclosed no residual left to right shunt but revealed moderate tricuspid valve insufficiency. In Case 6 catheterization data demonstrated no residual shunt or pulmonic stenosis, but the left ventriculogram revealed persistent ballooning of the mitral valve with minimal insufficiency.

Discussion

Griffith[13] in 1892 first suggested that late apical systolic murmurs were due to mitral valve insufficiency, but it was not until 1963 that Barlow et al.[14] confirmed this observation by angiocardiography. The mitral origin of these characteristic murmurs and the frequently associated midsystolic click was also documented by phonocardiography.[15–17] The relation of these findings to prolapse of the valve was almost simultaneously reported by Barlow and Bosman[1] and by Criley et al.,[18] who found that the systolic click coincided with the maximal projection of the prolapsed valve into the left atrium. Reid[19] has theorized that the clicks are caused by "chordal snap" due to sudden tensing of the chordae tendineae. Four of our patients with an ostium secundum atrial septal defect had auscultatory findings suggesting an abnormal mitral valve. Three had an apical systolic click; one of these and another patient also had a late systolic murmur of mitral insufficiency. In Case 4 this murmur was detectable only when the patient was seated.[20] These observations indicate that careful apical auscultation with the patient in different positions should be performed in any case of atrial septal defect.

Differentiation from ostium primum defect: The electrocardiograms and vectorcardiograms were unusual for a secundum type of atrial defect. They were of particular significance in Patients 1 and 3, who had no detectable apical clicks or murmurs but who had a superior mean QRS axis or leftward and predominantly counterclockwise frontal QRS loops, or both. Patients 4 and 5 also had abnormal negative T waves in the left precordial leads, as previously described in patients with balloon mitral valve.[21]

These unexpected electrovectorcardiographic and apical auscultatory findings led to the erroneous clinical diagnosis of ostium primum atrial septal defect in six of our patients. The correct anatomy was confirmed by selective angiocardiography, which demonstrated that all patients had a normal left ventricular outflow tract (thus ruling out the presence of an endocardial cushion defect) as well as manifestations of ballooning mitral leaflets. The latter ranged from discrete protrusions on either side of the base of the left ventricle to gross deformity of both leaflets with dilatation of the mitral annulus.[22] In addition, areas of asynergistic contraction of the left ventricle were

commonly present. They manifested as an abnormal bulging in the midportion of the anterolateral wall or as an indentation of the inferoposterior wall into the left ventricular inflow tract.[23] Ehlers et al.[24] believe that the latter phenomenon is the result of a congenital anomaly in a localized area of the left ventricular myocardium, similar to the one recently described after myocardial infarction.[25] Grossman et al.[26] have postulated that when this indentation occurs the chordae attached to the posterior papillary muscle become slack, allowing the posterior mitral leaflet to balloon into the left atrium. Despite the segmental myocardial dysfunction the overall left ventricular performance is normal.[27]

The anatomic characteristics of the malformed mitral valve, with redundant leaflets and elongation of the chordae tendineae, have been observed at operation,[2,22] as in three of our cases. There are also pathologic descriptions,[28] including one[29] in which similar changes were observed in the tricuspid valve, as in our Case 2.

Etiology and natural history: Several possible origins of the lesion have been suggested, including rheumatic,[14] traumatic[7] or localized ischemic[25,30] heart disease. This type of valve abnormality also has been commonly seen in patients with Marfan's syndrome.[2,5,7,18] None of these possibilities were definable in our patients, thus supporting a congenital origin of the mitral valve abnormality.

Little is known about the natural history of a congenital balloon mitral valve identified in childhood, although adults have been found to have significant complications as a result of similarly malformed atrioventricular valves. Dysfunction of the mitral apparatus may produce insufficiency[30] that, once established, may become progressively severe.[31] Infective endocarditis has been reported in several instances,[3,29,32] indicating the need for proper antibiotic prophylaxis, even when the valve is competent.[33] Significant cardiac arrhythmias, particularly those related to exercise, have been reported in up to 50 percent of cases.[34,35] In some instances these have been presumed to be the cause of sudden death.[5,8] Thus, identification of a balloon mitral valve has important prognostic significance. Furthermore, the association of a balloon mitral valve with an ostium secundum atrial septal defect must be differentiated from an endocardial cushion defect (ostium primum atrial septal defect).

Clinical implications: Since we became acutely aware of this combination of defects we have routinely performed a left ventriculogram in all patients with atrial septal defect. Seven of 10 consecutive patients examined had a balloon mitral valve. In two adults (aged 19 and 21 years, respectively) and in Patient 8 of this study no abnormality of the mitral valve was suspected clinically since there were no unusual electrovectorcardiographic observations or suggestive apical auscultatory findings.

In summary, we conclude that every patient with an atrial septal defect should have a left ventriculogram to determine the status of the mitral valve.

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Cyanosis in Patients with Atrial Septal Defect Due to Systemic Venous Drainage into the Left Atrium

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Cyanosis and clubbing of the digits in patients with atrial septal defect usually are indicative of reversal of the interatrial shunt consequent to reduced right ventricular compliance and severe pulmonary hypertension. The condition may be considered inoperable. The cases reported herein emphasize the occurrence of cyanosis in patients with interatrial communication and continued significant left to right shunting, as a consequence of systemic venoarterial shunting into the left atrium. Carefully planned cardiac catherization is indicated to detect the less well recognized mechanisms of cyanosis so that such patients are not denied the benefits of surgical closure of the septal defect.

Cyanosis, clubbing of the digits and erythrocytosis in patients with an atrial septal defect generally result from shunting of venous blood through the interatrial communication. Since reduced distensibility of the right ventricle, the result of obstructive pulmonary hypertension, is responsible in most instances,[1] cyanosis may be considered to contraindicate operative treatment.[2] It is not widely recognized that arterial oxygen desaturation can occur in the presence of normal pulmonary vascular resistance and predominant left to right shunting as a consequence of functional or anatomic diversion of systemic venous return into the left atrium.[3,4] Under these circumstances, cyanosis does not constitute a contraindication to operative closure of the atrial septal defect. Our report therefore emphasizes this cause of venoarterial shunting in order that it may be more frequently considered and specifically sought during diagnostic cardiac catheterization.

Case Reports

Case 1. Atrial Septal Defect with Streaming of Inferior Vena Caval Blood Across the Defect into Left Atrium

Two years before admission a 55 year old telephone cable installer noted the onset of progressive dyspnea on exertion, a cough productive of clear sputum, and cyanosis of the nail beds. He denied chest pain, syncope or palpitations and had been unaware of any cardiac abnormality. He had smoked two packages of cigarettes daily for 20 years.

On physical examination, his face was plethoric and his lips and nailbeds were cyanotic. Neither his fingers nor his toes were clubbed. Blood pressure was 160/100 mm Hg, pulse rate 112/min and regular. Bilateral inspiratory rales were present. The cardiac apical impulse was palpated in the fifth left intercostal space in the midclavicular line. The second heart sound was widely split and remained split throughout the respiratory cycle. Subsequent phonocardiograms documented an increase in splitting of 15 msec during inspiration. Both atrial and ventricular diastolic gallops were audible. A grade 2/6 systolic ejection murmur was heard in the second left intercostal space; there was no diastolic murmur.

Hemoglobin was 19.2 g/100 ml and hematocrit 58 percent. Electrocardiograms revealed atrial tachycardia with 2:1 block resulting in a ventricular response of 100 beats/min; the mean QRS axis was vertical. Chest roentgeno-

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grams disclosed cardiomegaly, pulmonary plethora and diffuse nodular infiltrates. Values for arterial blood gases, obtained with the patient at rest and breathing room air, were as follows: PaO_2 58 mm Hg (87 percent saturation calculated), $PaCO_2$ 32 mm Hg, pH 7.46. With exercise, the PaO_2 increased to 62 mm Hg (93 percent saturation calculated). While the patient was breathing 100 percent oxygen, the PaO_2 rose only to 200 mm Hg (99.6 percent saturation calculated). A right to left intracardiac shunt was suspected.

During cardiac catheterization by way of the right femoral vein the catheter was easily advanced from the right atrium across an atrial septal defect to the left atrium. The left atrial angiogram revealed a left to right shunt in the central portion of the atrial septum. The hemodynamic data (Tables I and II) were interpreted as showing a bidirectional shunt at the atrial level. Hydrogen gas inhalation performed with platinum electrodes in the left pulmonary and left femoral arteries indicated the presence of a left to right shunt (Fig. 1). Ascorbate was injected sequentially into the pulmonary artery, right ventricle, right atrium and inferior vena cava. A small right to left shunt was demonstrated by the polarographic recording obtained from the femoral artery after inferior caval injection[5] (Fig. 2).

At operation, a 3 cm ostium secundum atrial septal defect was found and repaired with a Dacron® patch. The valve of the inferior vena cava (Eustachian valve) was not enlarged. Tissue obtained from lung biopsy was interpreted as showing chronic pleuritis, emphysema and septal fibrosis. On the first postoperative day, normal sinus rhythm returned. The ejection systolic murmur and the cyanosis disappeared postoperatively.

Comment: Pulmonary arterial pressure and resistance were near normal. Arterial hypoxemia may have been due in part to pulmonary disease since pulmonary venous saturation was only 93 percent. Nevertheless, additional right to left shunting across the atrial septal defect was confirmed by the ascorbate dilution study and detection of a further decline in oxygen saturation in blood obtained from the left ventricle and systemic arteries.

Case 2. Atrial Septal Defect with Shunting of Inferior Vena Caval Blood Into Left Atrium

A 40 year old laborer was well until age 16 years when, after an illness characterized by fever, myalgia and arthralgia, he noted a decrease in exercise tolerance. At age 21, exertional dyspnea occurred and physical examination revealed cyanosis, digital clubbing, fixed splitting of the second heart sound and a heart murmur. The diagnosis rendered at that time is not documented. Six years later these findings led to a diagnosis of atrial septal defect. Arterial hypoxemia was taken as evidence of Eisenmenger's syndrome, and the lesions were considered inoperable. Cardiac catherization was not performed.

The dyspnea increased in severity and at age 34, the patient experienced retrosternal chest pain relieved with nitroglycerin. He was hospitalized because of a prolonged episode of chest pain and given digoxin therapy. Between ages 34 and 40, he had several hospitalizations for recurrent chest pain. On the last of these diagnostic cardiac catheterization was performed.

At the time of admission for catheterization physical examination revealed cyanosis of the lips and nail beds and clubbing of the fingers. Blood pressure was 140/90 mm Hg and pulse rate 100/min with occasional premature ventricular contractions. The chest was clear to percussion and auscultation. The cardiac apical impulse was palpated in the fifth left intercostal space 2 cm lateral to the midclavicular line. A left parasternal impulse and a systolic pulsation in the third left intercostal space were present. The second heart sound was narrowly split and did not vary. A grade 2/6 systolic ejection murmur was audible in the second left intercostal space radiating along the left sternal border to the apex.

Cardiac catheterization was performed by way of the right median basilic vein. The catheter was easily advanced into two pulmonary veins entering the right atrium as well

TABLE I

Cardiac Catheterization Data

	Case 1	Case 2		Case 3
		Preop	Postop	
A. Pressures (mm Hg)				
Left ventricle	165/6	102/12	...	90/16
Left atrium	(6)	(13)	...	(16)
Pulmonary vein	(6)	...	...	(16)
Pulmonary artery	35/14 (23)	80/32 (53)	56/23 (37)	70/30 (35)
Right ventricle	46/3	80/10	57/6	70/16
Right atrium	(6)	(13)	(6)	(16)
B. Oxygen Saturation (percent)				
Systemic artery	86	86	94	90
Left ventricle	87	...	...	89
Left atrium	93	89	...	88
Pulmonary vein	93	96	...	97
Pulmonary artery	83	76	83	...
Right ventricle	83	80	78	84
Right atrium				
High	65	78	70	...
Mid	68	79	78	...
Low	76	78	74	...
Superior vena cava	61	61	69	66
Inferior vena cava	65	...	76	79
Left superior vena cava	...	...	...	66

Figures in parentheses indicate mean pressures.
Postop = postoperative; preop = preoperative.

TABLE II

Calculated Indexes of Flow and Resistance

	Case 1	Case 2	Case 3
Pulmonary to systemic flow ratio	2.3/1	1.5/1	1.7/1
Left to right shunt as % of pulmonary blood flow	65%	50%	55%
Right to left shunt as % of systemic blood flow	25%	35%	25%
Pulmonary vascular resistance*	1.8†	6.4†	2.4

* $(\overline{PA} - \overline{LA})$/pulmonary blood flow (Wood's units).
† Normal oxygen consumption assumed in the calculation.

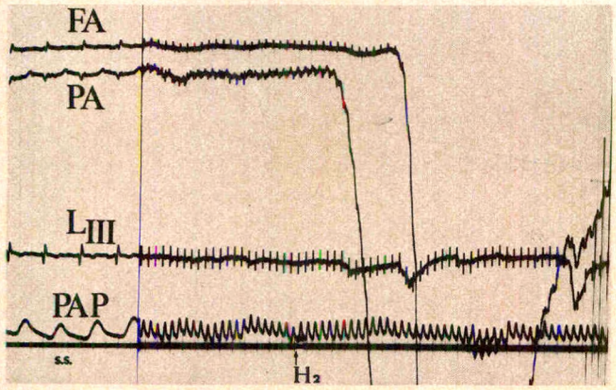

FIGURE 1. Case 1. Polarographic recordings from the femoral artery (FA) and pulmonary artery (PA) after inhalation of hydrogen gas (H_2). The hydrogen is first detected by the pulmonary arterial electrode indicating a left to right shunt. L_{III} = lead III of the electrocardiogram; PAP = pulmonary arterial pressure.

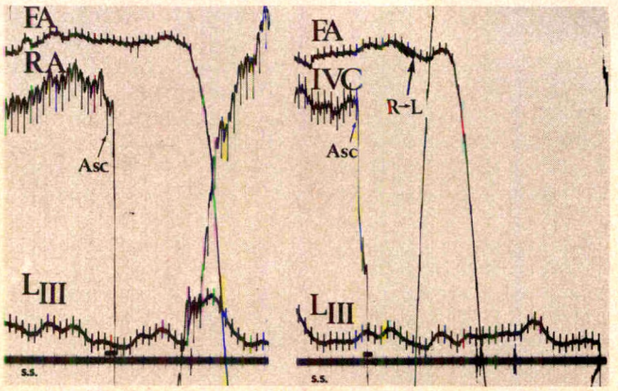

FIGURE 2. Case 1. Polarographic recordings from the femoral artery (FA) after injection of ascrobate (Asc) into the right atrium (RA) and inferior vena cava (IVC). A right to left (R → L) shunt is only seen after injection into the inferior vena cava.

as across an atrial septal defect to the left atrium. Indicator-dilution curves were performed. Blood was drawn from the brachial artery after injections of indocyanine green into both the inferior and the superior venae cavae. The curve obtained after injection into the inferior vena cava revealed two peaks, an early peak at 6 1/2 seconds and a late peak at 15 1/4 seconds; the curve obtained after injection into the superior vena cava disclosed only the late peak at 15 3/4 seconds (Fig. 3). These curves are consistent with shunting of blood from the inferior vena cava, but not the superior vena cava, into the left atrium. Inferior vena caval angiography with injection of the contrast media at the junction of the inferior vena cava and right atrium confirmed this streaming into the left atrium.

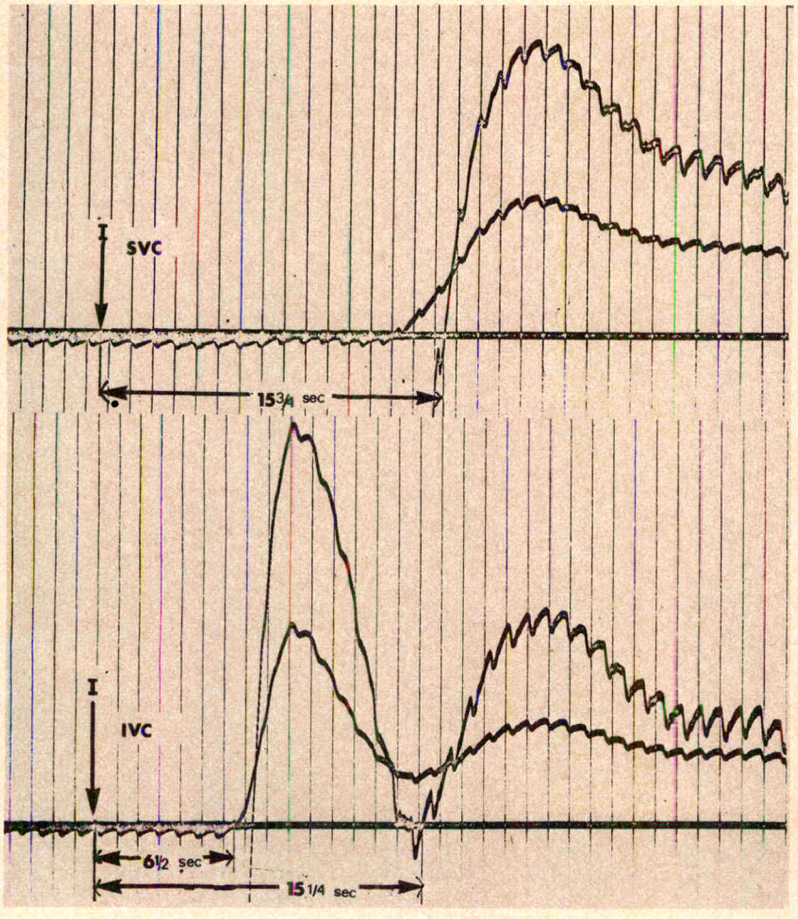

FIGURE 3. Case 2. Indicator-dilution curves recorded from the brachial artery after injection (I) of indocyanine green into the superior vena cava (SVC) **(top)** and the inferior vena cava (IVC) **(bottom).** The taller of each set of curves is the semilogarithmic replot; the smaller curve is the linear recording. See text for details.

Pressure measurements were made, oxygen saturation levels determined (Table I) and flow and resistance values calculated (Table II). The data were interpreted as indicating a bidirectional interatrial shunt and severe pulmonary hypertension. Results of coronary arteriography and left ventriculography performed 1 week later were normal.

At operation, a 3 by 4 cm ostium secundum atrial septal defect associated with two pulmonary veins draining anomalously into the right atrium was found. The valve of the inferior vena cava was not abnormally large. The atrial septal defect was repaired with a Teflon® patch, and the anomalous pulmonary veins were directed into the left atrium.

The murmur and cyanosis disappeared postoperatively. Repeat cardiac catheterization was performed 3 months later. By means of hydrogen inhalation a small residual left to right interatrial communication was documented. Pulmonary arterial pressure had declined, but calculated pulmonary resistance was unchanged (Tables I and II).

Comment: The patient's prognosis is believed to be improved by operation although the long-term response of the pulmonary circulation is not known.

Case 3. Atrial Septal Defect with Persistent Left Superior Vena Cava Entering Left Atrium

A 48 year old itinerant burlesque comedian was admitted because of congestive heart failure and syncope. He had been told that he was cyanotic at birth. He experienced brief episodes of palpitations during childhood but denied any exercise limitation. At age 28 years, when a heart murmur was first heard, he was asymptomatic.

Cardiac catheterization was performed in another city 8 months before his present admission because of congestive heart failure and atrial fibrillation. The catheterization was performed by way of the right femoral artery and vein with use of the percutaneous technique. The venous catheter was easily advanced from the right atrium across an atrial septal defect into the left atrium. Pressures were measured, oxygen saturation levels determined (Table I) and values for flow and total pulmonary resistance calculated (Table II). These measurements were interpreted as indicating a predominant left to right shunt, a smaller right to left shunt, pulmonary hypertension and increased ventricular end-diastolic pressure.

After treatment with digoxin, diuretic agents and a low salt diet, the patient's condition improved, but 4 months before his present admission, after a period of dietary indiscretion, the congestive heart failure worsened and he had syncope for the first time. He was appropriately treated for heart failure and again became asymptomatic. One week before his present admission, he noted increased symptoms of congestive heart failure and on the day of admission he had a syncopal episode.

Physical examination revealed clubbing of the fingers and cyanosis of the lips and nail beds. Blood pressure was 120/70 mm Hg and pulse rate 80/min and irregular; respiratory rate was 25/min. Jugular venous distension was present to the angle of the mandible with the patient seated upright; prominent *v* waves were seen. Inspiratory rales were heard over both lung fields. The cardiac apex impulse was palpated in the fifth left intercostal space at the anterior axillary line. A left parasternal impulse was present. The second heart sound was physiologically split. A pansystolic murmur that increased in intensity during inspiration was audible at the lower left sternal border and radiated to the apex; a systolic ejection murmur was heard in the second left intercostal space. The liver span was 20 cm by percussion in the midclavicular line, and the spleen tip was palpable. Pitting edema and stasis dermatitis were present in both legs.

Hemogram revealed leukocyte count 3,000 cells/mm^3 with a normal differential; hemoglobin was 12.7 g/100 ml and hematocrit 39.0 percent. Values for arterial blood gases were pH 7.48, $PaCO_2$ 37 mm Hg, PaO_2 55 mm Hg (89 percent saturation calculated). Chest roentgenograms disclosed cardiomegaly, enlarged pulmonary arteries, an inconspicuous aortic knob and bilateral alveolar and interstitial infiltrates. Electrocardiograms revealed right bundle branch block, right axis deviation, right ventricular hypertrophy and atrial fibrillation.

The congestive heart failure was treated with digoxin, furosemide and oxygen. The patient was given anticoagulant therapy because of a clinical diagnosis of pulmonary emboli. The hospital course was downhill, and he died on the 12th hospital day after having major seizures and becoming aphasic.

Postmortem examination revealed a large atrial septal defect involving the posterior aspect of the atrial septum, a persistent left superior vena cava entering the left atrium, and absence of the coronary sinus. The heart weighed 950 g, and there was biatrial and biventricular hypertrophy.

Comment: The patient's life style prevented his obtaining appropriate medical care until the situation was far advanced. Operation was not contraindicated and might have been helpful had it been undertaken after cardiac catheterization 8 months before death. The onset of cyanosis in infancy was no doubt due to the venoarterial shunting from the anomalous systemic venous connection to the left atrium.

Discussion

In 1949 Selzer and Lewis[6] called attention to patients with atrial septal defect who had cyanosis unassociated with pulmonary hypertension or pulmonic stenosis. Reporting on 12 such patients, 2 with cyanosis since birth, they postulated functional drainage of systemic venous blood into the left atrium as the mechanism of cyanosis. Their conclusion was supported by the dye-dilution studies of Swan et al.,[7] which detected right to left shunting of small amounts of caval blood through interatrial communications in certain patients with a predominant left to right shunt. The quantity of such mixing usually did not result in clinical cyanosis.

Renewed interest in the anatomy of the right atrium generated by the introduction of surgical techniques to repair atrial septal defects led to the recognition of certain anatomic variations that appear to favor passage of inferior vena caval inflow into the left atrium.[8,9] Persistence of a large right valve of the sinus venosus (valve of the inferior vena cava, Eustachian valve) was shown to result in the deflection of a sufficient volume of venous blood into the left heart chambers to produce clinical cyanosis.[3] Others observed that the lower rim of ostium secundum defects was at times deficient. As viewed at operation this situation, attributable to excessive resorption of the ostium primum, was characterized by apparent continuity of the medial wall of the inferior vena cava with the inferior wall of the left atrium and by overriding of the caval inflow by the atrial septum.[9] Although

cases documenting clinical cyanosis from this abnormality have not to our knowledge been reported, it appears to be a possible mechanism.

In our two patients who were operated on, these anatomic aberrations were not detected. Neither were they reported by Winters et al.[10] in their description of two instances of cyanosis in patients with atrial septal defect, cyanosis and rather normal right heart pressures. Their cases and ours suggest that other anatomic alterations may account for cyanosis in some of these patients. Moreover, reduced right ventricular compliance not severe enough to result in balanced or reversed shunting may favor this pattern of flow in instances with unrecognized subtle structural peculiarities.

Our third case appears to be an example of a rare entity described by Raghib et al.[4] They described a developmental triad consisting of a persistent left superior vena cava terminating in the left atrium, absence of the coronary sinus, and an atrial septal defect involving the posteroinferior angle of the atrial septum. They attributed the three coexisting anomalies to failure of complete formation of the left atrioventricular fold, the fold that normally develops along the left side of the junction of the sinus venosus and the atrial portion of the heart.

Our three cases are additional examples of the occurrence of cyanosis despite persistent significant left to right shunting. In two patients streaming of the inferior caval blood across the atrial defect probably accounted for the venoarterial shunting. Altered right ventricular compliance may have been a factor favoring such a flow pattern in Case 2. The third case exhibited a rather rare type of congenital anomalous venous connection that resulted in the return of venous blood to the left atrium. We thus emphasize that the presence of cyanosis in patients with atrial septal defect cannot be used as infallible evidence of balanced or net right to left shunting, thereby constituting a contraindication to surgical closure of the defect. Carefully planned cardiac catheterization is indicated to detect the less well known mechanisms of cyanosis.

Acknowledgment

We thank George A. Kelser, Jr., MD for allowing us to include Case 1. We also appreciate the generosity of A. A. Douglas Moore, MD of Norfolk, Va. in providing the cardiac catheterization data in Case 3.

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Patency of Aortocoronary Vein Grafts and Serum Triglycerides

Three Year Follow-Up Study

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Fasting blood lipid levels were determined before operation and 1 and 3 years after operation in 36 patients to verify the hypothesis that hypertriglyceridemia plays a role in the fate of aortocoronary vein grafts. Graft patency was evaluated with use of arteriography 2 weeks, 1 year and 3 years after operation. Results of these studies show that patients with hypertriglyceridemia have a higher risk of occlusion or stenosis of vein grafts. Serum cholesterol levels do not appear to affect the fate of the grafts.

Serum triglyceride concentration was correlated with the fate of aortocoronary vein grafts 2 weeks and 1 year after operation in previous studies from our laboratory.[1] The findings suggested that triglyceride levels play an important role in the occlusion or reduction of the caliber of vein grafts. In this investigation we attempted to verify this hypothesis in 36 patients who had serial lipid analyses and angiographic evaluations before operation and 1 and 3 years after operation. If the hypothesis is valid, a low level of triglycerides should be associated with long-term patency of the grafts. Our current data appear to strengthen this hypothesis.

Subjects and Methods

In the first study, 163 consecutive patients had blood lipid determinations and selective angiography 2 weeks after operation, and 82 were similarly studied 1 year later.[1] Of these 82 patients, 36 were restudied 3 years postoperatively and form the basis of this study. Seventeen of these patients had multiple grafts, and 19 had single grafts. These 36 patients are part of a larger series of patients studied angiographically 3 years postoperatively by Grondin et al.[2] and Lespérance et al.[3] The latter two studies demonstrated that no vein graft was further reduced in caliber between the 1st and 3rd years after operation and only 5 percent became occluded in this period. Thus, the 36 subjects described here probably represent a valid sample of the larger groups.[2,3]

Arteriography was performed by the technique described previously.[4] Fasting blood samples were collected on the morning of the angiographic studies before operation and 1 and 3 years after operation. Total serum cholesterol and triglycerides were assayed as in the previous report.[1]

Results

Of the 36 patients, 1 had occlusion of a single graft 3 years postoperatively. In 27 of the remaining 35 patients, no occlusion occurred in their single or multiple grafts. Eight patients with multiple grafts had occlusion in one graft 1 year postoperatively. Table I shows the mean serial triglyceride concentration for all patients studied. The triglyceride level was lower 1 year postoperatively than before operation ($P < 0.05$), as in the previous report.[1] This difference was believed to be secondary to a loss of weight.[1] The triglyceride values at 1 and 3 years were not significantly different. The triglyceride levels of patients with single and multiple grafts did not differ significantly in any of

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TABLE I

Serial Triglyceride Concentration (mg/100 ml) in 35 Patients* with Aortocoronary Vein Grafting† (mean and standard deviations)

	Postoperative	
Preoperative‡	1 Year	3 Years
232 ±97	211 ±115	182 ±91

* Six women and 29 men with a mean age of 49 ± 7 years.

† The patient whose single graft was occluded at 3 years had the following triglyceride values: 227, 215, 194.

‡ Analysis of variance showed this mean value to be greater ($P < 0.05$) than at 1 year and 3 years combined. No significant difference existed between the mean values at 1 and 3 years.

TABLE II

Serial Triglyceride Concentration (mg/100 ml) in 17 Patients with Multiple Grafts and 18 Patients with a Single Graft* (mean and standard deviation)

		Postoperative		Mean for All 35 Patients in All Studies
Grafts†	Preoperative	1 Year	3 Years	
Multiple	251 ±100	230 ±100	201 ±99	203‡ ±91
Single	214 ± 89	194 ±126	165 ±79	

* One patient with a single graft occluded 3 years postoperatively is omitted (see Table I).

† Values for patients with multiple and single grafts did not differ significantly (Student *t* test).

‡ The mean value for the 27 patients with patent grafts in all studies was 186 ± 82 mg/100 ml 3 years postoperatively.

TABLE III

Serial Serum Cholesterol Concentration (mg/100 ml) in 35 Patients with Aortocoronary Vein Grafts (means and standard deviations)

	Postoperative	
Preoperative	1 Year	3 Years
243 ±49	240 ±51	246 ±57

the three studies. Table II shows that the mean concentration of triglycerides for all patients in all three studies was 203 ± 91 (standard deviation) mg/100 ml.

In the 27 patients whose grafts remained patent during the 3 year period, this mean value was 186 ± 82 mg/100 ml (Table II). The cholesterol level in these patients did not change during the 3 year period and was 246 ± 57 mg/100 ml at 3 years (Table III).

Discussion

Occlusion of aortocoronary vein grafts is uncommon between 1 and 3 years after operation, and little or no reduction occurs in the diameter of the graft.[2,3] This finding is in sharp contrast with the relatively high rate of occlusion and the diffuse reduction in the caliber of the graft noted 1 year postoperatively. It has been shown[2] that in patients whose grafts are occluded 2 weeks after operation, the mean triglyceride level is higher (287 mg/100 ml) than that (235 mg/100 ml) of patients whose grafts are occluded later, 1 year after operation. The same study also demonstrated that the mean triglyceride level was significantly lower (181 mg/100 ml)[1] in patients who had patent grafts with little or no reduction of caliber at 1 year.[1] In our study, patients whose grafts were patent 3 years postoperatively had an overall mean triglyceride level of 186 ± 82 mg/100 ml (Table II).

Patients with the lowest serum triglyceride levels demonstrated patency of all their grafts in each of the three angiographic studies, and our findings suggest that patients with high triglyceride levels may be at greater risk of occlusion or stenosis of vein grafts during the first year after operation. This notion of risk implies that other factors[1,3,4] play a role in the fate of the vein graft. These factors may include the surgical technique itself, the quality of the artery grafted (diameter, degree of atherosclerosis, runoff) and the presence of stenosis at the site of anastomoses. The occlusion of grafts or the progressive reduction in their caliber may perhaps be prevented or minimized by a better selection of patients[5] and by improved surgical technique.[6] However, our results suggest that hypertriglyceridemia is a factor that should be taken into consideration and corrected. Patients may benefit from a reduction in serum triglycerides before and after myocardial revascularization. The possible mechanisms by which hypertriglyceridemia influences the fate of the aortocoronary vein grafts has been discussed previously.[1]

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Chordae Tendineae Rupture Complicating the Systolic Click-Late Systolic Murmur Syndrome

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In a patient with a documented nonejection systolic click and late systolic murmur, acute mitral insufficiency developed as a result of spontaneous rupture of mitral chordae tendineae. There was no evidence of previous endocarditis, rheumatic fever or congenital heart disease. The ballooning mitral valve syndrome has previously been considered relatively benign. Chordal rupture has been predicted, and presumptive cases have been alluded to by several investigators. This well documented report of such a complication casts further doubt on the benignity of the syndrome.

The prognosis of patients with a mid-systolic click and late systolic murmur due to abnormalities of the mitral valve apparatus was initially thought to be benign. A number of complications are now known to occur in these patients, casting considerable doubt upon the benignity of the lesion. Spontaneous chordal rupture with resulting acute severe mitral insufficiency has been predicted in this syndrome[1–4] but, although alluded to in several reports,[5,6] this complication is not generally well known and the clinical course has not been documented. In this report we document the development of acute mitral insufficiency due to ruptured chordae tendineae in an asymptomatic patient with the nonejection systolic click-late systolic murmur syndrome; the condition resulted in severe congestive heart failure requiring urgent surgery. The rapid evolution of this severe hemodynamic disturbance emphasizes one of the potential serious complications of this syndrome.

Case Report

A 52 year old woman consulted a cardiologist in 1967 because of chest pain of the anginal type. The symptoms had been mild and infrequent, occurring only three to four times a year in relation to stress or fatigue. She had been taking coronary vasodilating agents and had been able to work as a clinic nurse without difficulty. Years previously she had been given procainamide for troublesome palpitations which had subsided spontaneously. She had knowledge of a heart murmur since age 23 but had no history of rheumatic fever. Physical examination at this time was noncontributory except for a prominent mid-systolic click and a grade 2/6 late systolic murmur heard at the apex. There was no evidence of cardiac enlargement or congestive heart failure. Subsequently she continued to take coronary vasodilating agents, and the click and murmur were heard at each of approximately 12 examinations during the next 5 1/2 years by the same observer. Periodic electrocardiograms were essentially normal and did not change.

In December 1971 left lingular pneumonia developed with pneumococcus isolated from sputum, and negative blood cultures. Her attending internist noted the cardiac findings and phonocardiography was performed (Fig. 1). She made an uneventful recovery, and auscultatory findings continued unchanged.

In March 1973 at age 58, she had fever of 102° F and a cough producing thick yellow blood-streaked sputum. Chest X-ray films showed extensive infiltrate fanning out from the right hilum involving the right middle and lower

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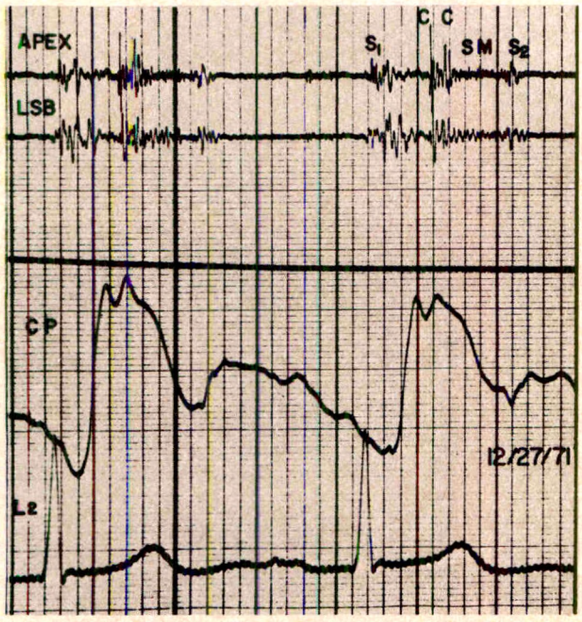

FIGURE 1. Phonocardiogram recorded at the apex and left sternal border (LSB) in December 1971 during an episode of bronchopneumonia. A double nonejection systolic click (C) is present, followed by a late systolic murmur (SM). CP = carotid arterial pulse; L_2 = lead II of the electrocardiogram.

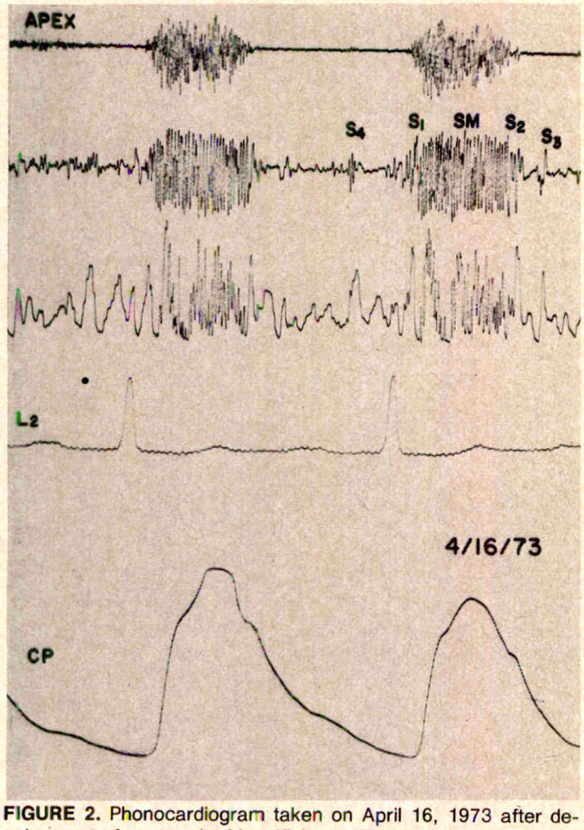

FIGURE 2. Phonocardiogram taken on April 16, 1973 after development of acute mitral insufficiency. The murmur (SM) is now pansystolic, and there are prominent atrial (S_4) and ventricular (S_3) gallops.

pulmonary lobes, consistent with bronchopneumonia. Physical examination revealed a dramatic change in the murmur, which was now grade 6/6, pansystolic, blowing and radiating widely throughout the precordium and to the back, accompanied by a systolic thrill. A loud ventricular third sound gallop was present, and the systolic click was no longer heard. There were no stigmata of bacterial endocarditis at this time or subsequently and results of five blood cultures were negative. Sputum culture grew no pathogens. Peripheral blood examination showed only mild leukocytosis and no leftward shift. Results of lung radioisotope scan were consistent with pneumonia or pulmonary embolism, or both. The electrocardiogram now showed a rightward shift of the electrical axis and probable left ventricular hypertrophy.

Treatment with antibiotic agents and heparin was started, and digitalis and diuretic agents were given because of the development of congestive heart failure and atrial fibrillation. She rapidly became afebrile, had a significant diuresis and the atrial fibrillation reverted to normal sinus rhythm. The murmur and gallop remained loud after discharge, however, and she was readmitted for further studies because of marked respiratory distress including paroxysmal nocturnal dyspnea.

Phonocardiography confirmed the pansystolic murmur and the atrial and ventricular gallops (Fig. 2). *Cardiac catheterization* data were consistent with acute mitral insufficiency, revealing an increased mean wedge pressure of 30 mm Hg, massive *V* waves of 60 mm Hg and pulmonary hypertension. Angiograms disclosed slight enlargement of the left ventricle and left atrium with 4+ mitral regurgitation. The posterior leaflet of the mitral valve was thin, not calcified and very mobile, ballooning into the left atrium during systole (Fig. 3). The aortic valve and right and left coronary arteries were normal.

Mitral valve replacement was undertaken because of persistent class IV (New York Heart Association classification) symptoms despite intensive medical therapy. At operation, the mitral valve leaflets were intact, smooth, thin and mobile with no lesions suggesting previous endocarditis. Three avulsed chordae to the central portion of the posterior leaflet were noted. The mitral valve was replaced with a Cooley-Cutter prosthesis. Postoperatively hypoten-

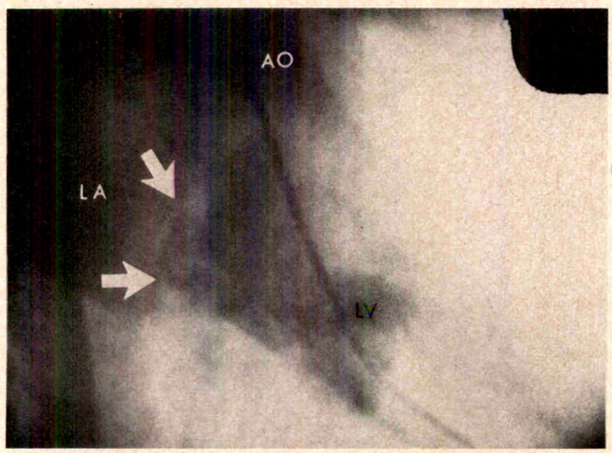

FIGURE 3. Left ventricular angiogram in right anterior oblique projection. The posterior mitral valve leaflet is seen ballooning into the left atrium (LA) during systole **(arrows).** The left atrium is heavily opacified as a result of the massive mitral regurgitation. AO = aorta; LV = left ventricle.

sion and severe bradycardia developed. Reoperation was attempted to control bleeding after medical measures had failed, but the patient died.

Autopsy findings disclosed no additional congenital or acquired heart defects, stigmata of endocarditis or evidence of healed rheumatic heart disease. Special staining of leaflet tissue did not show myxomatous or mucoid changes.

Two of the patient's five children were examined and one, a 27 year old daughter, had a systolic click and murmur documented by phonocardiography.

Discussion

The syndrome of the systolic click-late systolic murmur has been recognized for at least a decade. Diverse causes have been postulated for the mild mitral insufficiency, including rheumatic fever, healed endocarditis, trauma, connective tissue disorders, atheromatous involvement of leaflets and chordae, cardiomyopathy and ischemic papillary muscle dysfunction.[1,7–12] In many patients no underlying cause is demonstrable, but hemodynamic and pathologic evidence for the valvular and chordal dyskinesis has been demonstrated by an abnormally large mitral annulus,[9,12,13] asynergy of left ventricular contraction[10,13,14] and a ground substance abnormality in the valve leaflet.[15] A familial occurrence is also well documented.[9,10,16–19]

Prognosis: Patients with auscultatory findings of prolapsing mitral valve leaflets and mild mitral insufficiency without other complicating heart disease have been thought to have a relatively good prognosis. Segal and Likoff[20] studied eight patients with mild exertional dyspnea and rapid irregular heartbeat and concluded that the click-murmur syndrome was innocent. Engle[12] stated that the syndrome was benign although the patients she described had T wave abnormalities on the electrocardiogram. Hancock and Cohn[7] described 40 patients with the syndrome, some of whom complained of palpitations, mild dyspnea and atypical chest pain. These investigators documented atrial and ventricular arrhythmias in several patients and an R on T phenomenon in one patient who died suddenly. They concluded that the prognosis was favorable except in patients with arrhythmias.

Barlow et al.[2] alluded to sudden death in patients with abnormal electrocardiograms and arrhythmias and stated the prognosis must be guarded in such patients. Gooch et al.[14] and Pocock and Barlow[9,22] commented on the emergence of serious arrhythmias after exercise testing in patients with the syndrome, and considered suppression of the arrhythmias important enough to warrant use of antiarrhythmic drugs.

Potential complication of chordal rupture and acute mitral regurgitation: Streptococcus viridans endocarditis has been reported in patients with the click-murmur syndrome[7,17,23] and in a patient with only a click who had a transient late systolic murmur during the acute phase of the infection,[24] and antibiotic prophylaxis was recommended on this basis. However, Stannard et al.[16] in describing 13 patients with no symptoms of cardiac decompensation noted that the majority had had teeth extracted without developing bacterial endocarditis. Criley et al.[1] and Barlow et al.[2] predicted that the minimal mitral regurgitation might be self-perpetuating and might progress after many years to severe valvular incompetence with or without ruptured chordae, on the principle that mitral insufficiency begets mitral insufficiency. Cobbs[3] stated that despite lack of suitable linear follow-up studies, patients with the syndrome constitute a significant reservoir for spontaneous chordal rupture developing after two or more decades.

Singh et al.,[4] citing seven patients with spontaneous rupture of mitral chordae tendineae, mentioned two who had apical systolic murmurs for several years before the onset of acute mitral insufficiency. They stated that the long-term prognosis of the recently characterized floppy mitral valve syndrome was not sufficiently known to predict whether there would be a high rate of late spontaneous chordal rupture. Leachman and Cokkinos[5] described 19 patients operated upon for mitral regurgitation and found to have rupture of chordae to the posterior leaflet; 4 of these had a murmur dating from childhood or young adulthood and may have had a syndrome similar to that of our patient. These authors stated that the main complication of the syndrome seems to be its tendency to progress to massive mitral regurgitation due to chordal rupture, but they provided no documentation of prior and later findings constituting suitable linear follow-up of this lesion. Sloman et al.[6] followed up 50 patients with the syndrome and found 2 who had progressive regurgitation requiring surgery. Both had "flail" posterior mitral valve leaflets and ruptured chordae, and the authors postulated that the primary leaflet abnormality with secondary excessive chordal tension might be the predisposing cause of rupture.

In our patient we had clear clinical evidence of acute mitral insufficiency and searched for valvular perforation or chordal disruption, or both, by endocarditis as the most likely cause. Our patient had no laboratory or pathologic evidence for infection and no history or stigmata of a remote rheumatic process. Her prominent auscultatory pattern of ballooning mitral valve syndrome had been heard repeatedly and documented by phonocardiography before her acute cardiac decompensation.

We conclude that spontaneous rupture of chordae tendineae developed at the time of the acute febrile illness, with rapid progression from hemodynamically insignificant late mitral insufficiency to severe valvular regurgitation due to loss of chordal support to the posterior mitral valve leaflet. The carefully documented course of our patient leaves no doubt that the previously reported benignity of the systolic click-late systolic murmur syndrome is in question. The case emphasizes the serious potential complication of chordal rupture, in addition to the previously reported instances of not-so-benign fatal cardiac arrhythmias and bacterial endocarditis.

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Diastolic Blood Flow into the Pulmonary Artery in Carcinoid Heart Disease

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A patient with carcinoid heart disease manifested by mild pulmonary stenosis, severe tricuspid incompetence and mild tricuspid stenosis had unequivocal evidence of blood flow from the right ventricle into the pulmonary artery during ventricular diastole. Simultaneous right ventricular and pulmonary arterial pressure curves demonstrated that right ventricular diastolic pressure exceeded pulmonary arterial pressure during mid-diastole, indicating consistent mid-diastolic opening of the pulmonary valve. This was followed by a parallel increase in right ventricular and pulmonary arterial pressures throughout the rest of diastole. Right heart cineangiograms, obtained with right atrial dye injection, substantiated the pattern of flow from the right ventricle to the pulmonary artery during ventricular diastole. This previously unrecognized phenomenon is probably due to the combined effects of increased right atrial pressure, decreased right ventricular compliance and normal pulmonary arterial pressure.

Ordinarily there is no blood flow from the right ventricle to the pulmonary artery during ventricular diastole. However, such flow is theoretically possible in diseases characterized by increased right atrial pressure and decreased pulmonary arterial pressure, particularly if associated with a noncompliant right ventricle. This combination is typically encountered in carcinoid heart disease. Under such circumstances opening of the tricuspid valve will lead not only to right ventricular filling but also to blood flow into the pulmonary artery during ventricular diastole because of the existing right atrial-right ventricular-pulmonary artery diastolic gradient.

The cardiac lesions in carcinoid syndrome consist of endocardial fibrous plaques involving the pulmonary valve, tricuspid valve, right atrium, right ventricle, cardiac veins and, less commonly, the left heart chambers.[1–5] The most common hemodynamic sequelae are pulmonary valve disease, usually with mild stenosis, accompanied by tricuspid valve disease with predominant incompetence. Hemodynamic and angiographic data are available in a few patients with carcinoid heart disease, but there has been no mention of forward flow into the pulmonary artery during diastole in any of the reported cases. Recently, we observed a patient with unequivocal evidence of blood flow from the right ventricle to the pulmonary artery during diastole.

Case Report

A 45 year old Caucasian woman was evaluated at the University of Iowa Hospitals in February 1973 because of progressive fatigability, ankle edema, a 20 lb weight gain and an increase in abdominal girth during the preceding 9 months. The patient enjoyed perfect health until 3 years earlier when she noted attacks of watery diarrhea without abdominal cramping or urgency. Gastrointestinal examination and tests at that time revealed no abnormality, and the condition was diagnosed as functional bowel syndrome. Two years

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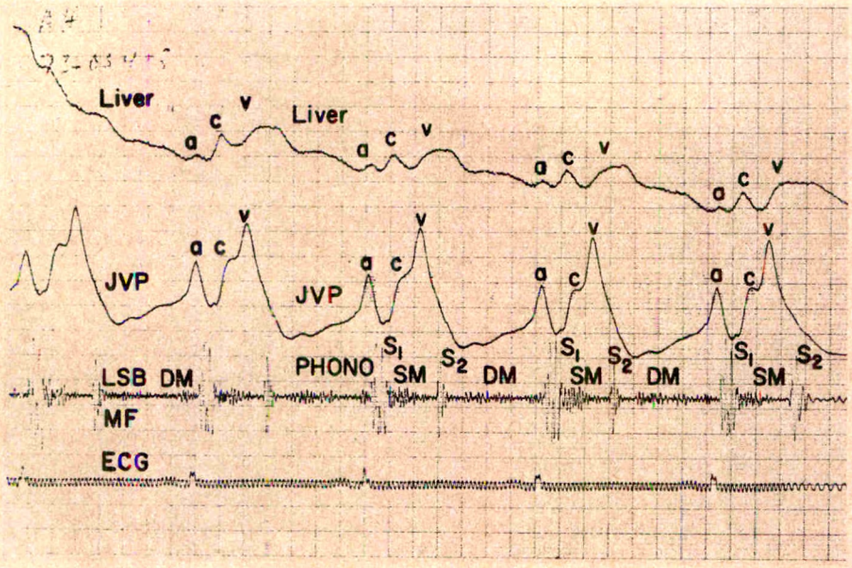

FIGURE 1. Simultaneous recordings of hepatic pulsations, jugular venous pulsations (JVP), phonocardiogram (PHONO) at left lower sternal border (LSB) and electrocardiogram (ECG). DM = diastolic murmur; MF = medium frequency; SM = systolic murmur.

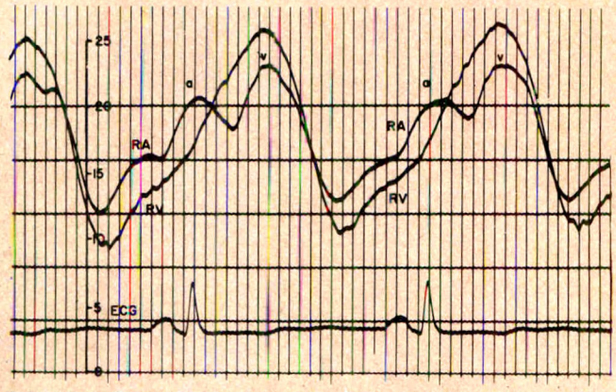

FIGURE 2. Simultaneous right atrial (RA) and right ventricular (RV) pressure tracings. Note the similar systolic wave form in both tracings, the diastolic atrioventricular gradient and the prominent *A* wave in the right atrial pressure tracing.

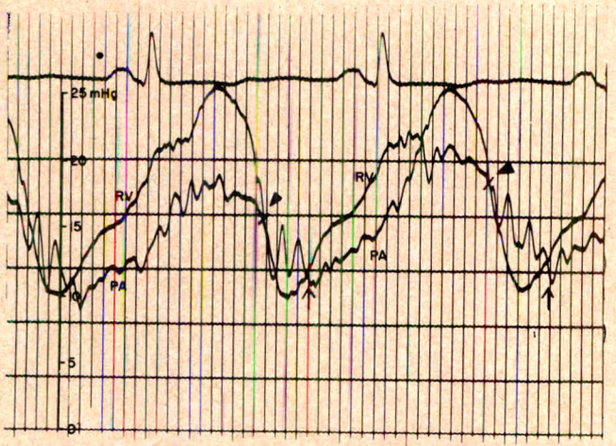

FIGURE 3. Simultaneous right ventricular (RV) and pulmonary arterial (PA) pressure tracings. Note the timing of pulmonary valve closure **(arrowhead)** and the diastolic opening of the pulmonary valve **(arrow)**, after which the increase in pulmonary pressure parallels that in right ventricular diastolic pressure.

later she noted minor daily flushing which she attributed to impending menopause; the flushing was not related to exertion, meals or excitement. The patient did not experience wheezing. No cardiac murmurs had been noted previously.

Examination revealed an alert woman in no distress, a regular pulse of 72 beats/min, blood pressure of 124/76 mm Hg, and a jugular venous pressure of 20 cm water with prominent *A* and *V* waves (Fig. 1). Carotid and peripheral pulses were normal. Cardiac examination revealed no left ventricular enlargement, a diastolic and a gentle early systolic left parasternal impulse, normal heart sounds, a grade 2/6 systolic murmur and a grade 2/6 diastolic rumble heard at the left lower sternal border (Fig. 1). Both murmurs increased with inspiration. The liver was tender and pulsatile and had a span of 15 cm in the right midclavicular line. The spleen was not palpable and there was questionable ascites. Both legs showed distal tense, brawny edema. Laboratory data revealed mild normocytic anemia, normal functioning of the liver and kidney and normal serum protein values. Twenty-four hour urinary 5-hydroxyindolacetic acid values were 98 and 127 mg in two collections (normal <10 mg). An electrocardiogram showed nonspecific ST–T changes and the chest X-ray films were noncontributory. A filling defect in the terminal ileum was seen on intestinal roentgenograms, and a liver radioisotope scan showed multiple filling defects.

Cardiac catheterization was performed because the patient's disabling symptoms were almost entirely cardiac in origin and tricuspid valve replacement was being considered. Simultaneous right atrial and right ventricular pressure curves (Fig. 2) and simultaneous right ventricular and pulmonary arterial pressure curves (Fig. 3) were obtained using catheters of equal bore diameter (no. 6F) and length and equisensitive simultaneously calibrated transducers. Reversing catheter connections yielded identical tracings. Hemodynamic findings (Table I) indicated a low cardiac index, normal pulmonary arterial pressure, mild pulmonary and tricuspid valve stenosis but normal left ventricular findings. Simultaneous pressure tracings showed reduced right ventricular pressure compared to pulmonary arterial pressure in early diastole, but soon thereafter right ventricular pressure exceeded pulmonary arterial diastolic

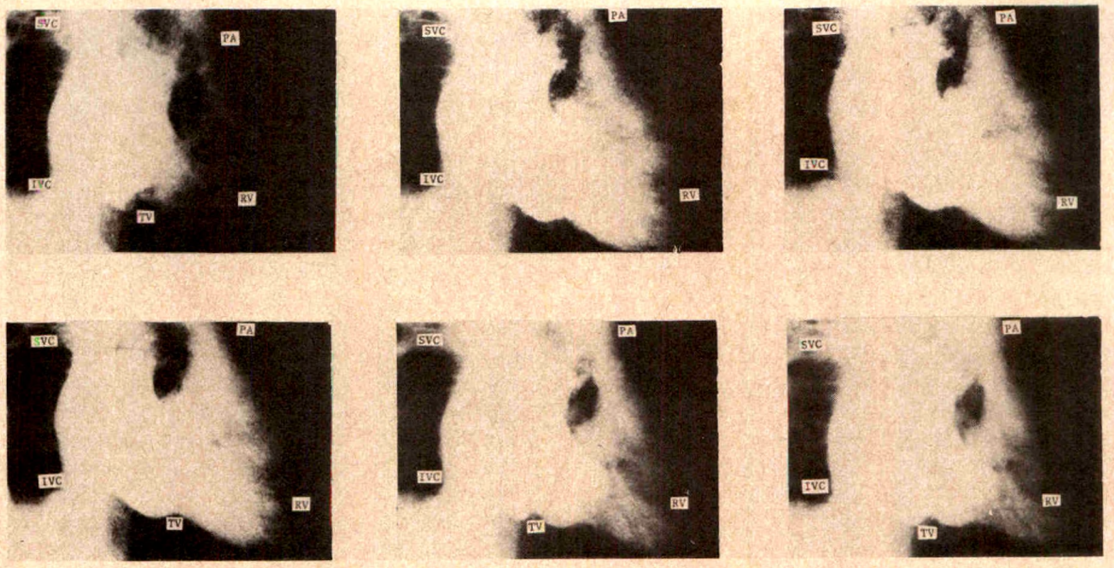

FIGURE 4. Cineangiographic frames obtained by dye injection into the right atrium. **Upper row,** during ventricular diastole (frames 1, 8, 15); **lower row,** during ventricular systole (frames 22, 29, 32). Note the flow of dye into the pulmonary artery during ventricular diastole. Cineangiograms filmed at 32 frames/sec. Heart rate during injection 64 beats/min. IVC = inferior vena cava; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

pressure, thereby indicating pulmonary valve opening at a pressure of 12 mm Hg (Fig. 3). For the rest of diastole pulmonary arterial pressure increased in parallel with the pressure rise in the right atrium and ventricle. Using a no. 8 angio-catheter, 60 ml of Renografin-76® was injected into the right atrium at a rate of 20 ml/sec and cineangiograms were filmed at a rate of 32 frames/sec in the right anterior oblique projection using a Phillips 9 inch image intensifier. Injection of dye into the right atrium produced opacification of that chamber. With the opening of the tricuspid valve in ventricular diastole, there was prompt opacification of the right ventricle and, within a small fraction of a second, the pulmonary artery, distinctly before the onset of ventricular systole (Fig. 4).

The day after cardiac catheterization, the patient suddenly collapsed upon arising from bed. Nausea and vomiting developed, as well as an intense cutaneous flush and generalized edema. The blood pressure became imperceptible. Her condition improved gradually with rapid intravenous administration of saline solution. Subsequently she has had several severe attacks of flushing, mainly related to standing. Methylprednisone was not of substantial help, but the noncardiac manifestations of disease responded favorably to a combination of antineoplastic agents (streptozotocin and 5-fluorouracil). Cardiac surgery has been deferred but may need to be reconsidered if the patient's chief symptoms continue to be related to cardiac involvement.

Discussion

In our patient, right ventricular to pulmonary artery blood flow during ventricular diastole was demonstrated by simultaneous right ventricular and pulmonary arterial pressure curves, as well as by right heart cineangiograms utilizing right atrial dye injection. Although this phenomenon has not been emphasized previously, available data in reported cases of carcinoid heart disease strongly suggest a similar hemodynamic situation in some of these patients.[5–8]

TABLE I

Hemodynamic Findings

Variables	Values
Pressures (mm Hg)	
Right atrial (RA)	$a = 21$, $v = 23$ (18)
Right ventricular (RV) systolic/end-diastolic	26/18
Pulmonary arterial (PA)	22/10 (14)
Pulmonary wedge	(9)
Left ventricular systolic/end-diastolic	115/12
Femoral arterial	115/70 (90)
Pressure gradients (mm Hg)	
RA-RV	
0.1 second diastolic	1
End-diastolic	2
RV-PA	
Mean systolic	4
Peak systolic	6
Blood gases	
O_2 consumption	
(ml)	176
(ml/m²)	103
Arteriovenous O_2 difference (vol. %)	6.5
Cardiac output (liters/min)	3.0
Cardiac index (liters/min per m²)	1.8
Left ventricular volumes (ml)	
End-diastolic	88
End-systolic	33
Ejection fraction	0.62

Figures in parentheses indicate mean values.

Four of 11 patients studied by Trell et al.[5] and the patient described by Wright and Mulder[6] had right ventricular end-diastolic pressure greater than the corresponding pulmonary arterial diastolic pressure. The patient described by Levine and Folse[7] and that by Rokseth and Sanderud[8] had right ventricular pressure curves very similar to those of our case, but simultaneous recordings with pulmonary arterial pressure are not available in these patients.

The association of this phenomenon with carcinoid heart disease may be related to a combination of factors including: (1) increased right atrial pressure due to the added effects of severe tricuspid regurgitation, relatively mild tricuspid stenosis and decreased right atrial compliance, (2) decreased right ventricular compliance due to subendocardial fibrosis, and (3) normal pulmonary arterial pressure. It is possible that blood flow into the pulmonary artery during diastole occurs not only in carcinoid heart disease but also in conditions characterized by increased right atrial pressure and normal pulmonary arterial pressure, such as Ebstein's disease and other congenital or acquired anomalies of the tricuspid valve. It has been shown that pulmonary arterial pressure tracings in patients with Ebstein's disease may show a presystolic positive wave coincident with atrial contraction,[9] which suggests presystolic blood flow into the pulmonary artery.

Theoretically, angiographic evidence of blood flow from the right atrium to the right ventricle to the pulmonary artery during diastole in our patient might have been augmented artifactually by an increase in atrial pressure caused by the injection of dye into the right atrium. Although data on atrial pressure were not obtained in our patient, in our laboratory right atrial injection by the method used in this study has not increased mean right atrial pressure by more than 3 mm Hg, nor has it altered pulmonary arterial pressure significantly. Furthermore, the angiographic findings in our case were consistent with hemodynamic data indicating a genuine diastolic pressure gradient between the right ventricle and pulmonary artery.

The main presenting features in our case were related to cardiac lesions rather than the underlying disease, an unusual finding in patients with the carcinoid syndrome.[8] An almost fatal episode of flushing and tissue edema that occurred shortly after cardiac catheterization and angiocardiography may have been coincidental; however, it is likely that cardiac catheterization and angiography were somehow responsible, since these procedures are occasionally followed by fatal complications.[10,11] Cardiac catheterization and angiography should be reserved for patients being considered for cardiac surgery or those in whom there is a question regarding the nature of cardiac disease.[12,13]

Acknowledgment

We thank Dr. Allyn Mark for his helpful criticism.

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Calcium Responses ("Calcium Spikes")

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In 1961 Fleckenstein and his co-workers[1] in Freiburg, Germany, reported that adrenaline (5 μg/ml) restores contractility and excitability in amphibian and mammalian myocardium depolarized by potassium (12 to 23 millimoles/liter). These investigators showed that this restitution occurs without change in the resting membrane potential, which ranged from about −30 to −40 mv. The upstroke velocity of action potentials generated by adrenaline in such depolarized tissue was decreased, and the rate of impulse propagation was very slow. However, the overshoot of these action potentials was either normal, or even greater than normal. These unusual findings of Fleckenstein et al. could not be explained by the Hodgkin-Huxley ionic theory governing excitation in the giant squid axon,[2] and in cardiac Purkinje fibers.[3]

In the late 1960's cardiac electrophysiologists made three discoveries that contributed to our understanding of the mechanism of action potentials originating in depolarized myocardium: (1) identification of the inward calcium current, (2) separation of the depolarizing currents into two channels, "rapid" and "slow," and (3) demonstration that the permeability of the calcium current carrying slow channel, is enhanced by adrenaline.

The principal credit for the identification and characterization of the slow inward calcium current in mammalian Purkinje and ventricular myocardial fibers belongs to Reuter.[4–7] He and his co-worker Beeler[5,6] described the kinetics of the current and showed that in a sodium-free solution this current was activated at a threshold potential of about −30 to −40 mv. Reuter also demonstrated that adrenaline causes an increase in calcium influx through the depolarized myocardium.[4]

Role of Calcium in Adrenaline-Induced Depolarization

During the past decade several prominent cardiac electrophysiologists (cited in Ref 8) postulated that the upstroke of the cardiac action potential may be composed of two independent components, a rapid spike and a slower depolarization wave. Strong support of this idea has been provided by the recent voltage-clamp experiments in frog atrial trabeculae.[9] These experiments of Rougier et al.[9] have shown conclusively that the inward depolarizing membrane current flows through two separate "channels": a rapid, pure sodium channel and a slow "mixed" sodium-calcium channel. The rapid channel can be selectively blocked by tetrodotoxin, and the slow channel by manganese and lanthanides.[7,9] Vassort et al.[10] have shown that adrenaline activates the slow channel.

In 1969 Carmeliet and Vereecke[11] repeated and extended the original experiments of the Freiburg group using bovine Purkinje fibers. In their experiments, adrenaline induced propagated action potentials with a slow upstroke in sodium-free solutions and also when the rapid inward sodium current was inactivated by increased extracellular potassium concentration or tetrodotoxin. Such responses did not occur in calcium-free solutions unless calcium was substituted by another divalent ion such as strontium. These experiments confirmed the action of adrenaline on the slow channel and suggested that calcium current was responsible for the slow depolarization. In 1970 Pappano[12] demonstrated a strict mathematical correlation between the amplitude of spikes induced by depolarization and the external calcium concentration, and thereby established the predominant, if not the exclusive role of calcium in the production of adrenaline-dependent depolarizations. These studies justify the term "calcium spikes" for action potentials generated in tissue in which the rapid inward sodium current is inactivated. The effect of catecholamine on the "calcium spikes" is due to beta adrenergic action. Depolarized myocardium is more sensitive to isoproterenol than to adrenaline or noradrenaline, and the response is blocked by propranolol.[12] Caffeine and 3′5′ cyclic adenosine monophosphate (AMP) are also capable of inducing similar responses, but their action is weaker than that of catecholamines.[13,14]

Slow Calcium Responses and Cardiac Arrhythmias

The system of calcium-dependent depolarization appears to be ubiquitous in cardiac muscle since it has been demonstrated in many different types of cardiac fibers in different animal species, including a 9 to 13 day old chick embryo.[14] The unique features of the impulse propagation induced by this type of depolarization have been extensively investigated by Cranefield, Hoffman and Wit.[15–19] These investigators have shown that in canine Purkinje fibers depolarized by potassium, and treated with adrenaline,

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the conduction velocity may be as low as 1 percent of normal,[19] and that such slow conduction may be associated with one-way or two-way block, summation, inhibition, reentry and circus movement.[17,18] Cranefield and his colleagues[19] described in detail the differences between the characteristics of the fast and the slow responses and proved conclusively that the pathway for reentry and circus movement of the slow responses may be shorter than 1 cm. They[19] also suggested that acute myocardial ischemia could precipitate such reentrant arrhythmias because in this condition the localized depolarization and local release of catecholamines would create conditions particularly favorable to the appearance of slow responses.

Some of the reentrant arrhythmias produced in dogs with acute ischemia show evidence of very slow conduction.[20,21] This suggests that the depolarizations induced by calcium may, indeed, play an important role in the critical slowing of conduction in the ischemic or otherwise damaged myocardium.

Slow Calcium Response and Spontaneous Myocardial Depolarization

Another interesting problem emerging from the studies of calcium spikes concerns the possibility that slow depolarizations can induce spontaneous propagation of action potentials without the assistance of impulses generated by pacemaker activity in other parts of the heart. Cranefield et al.[19] have pointed out that in most experiments the slow response has been stimulus-dependent. However, spontaneous activity in a depolarized myocardium has been observed. Imanishi[22] showed a rapid succession of calcium-dependent depolarizations in cardiac Purkinje fibers after depolarizations induced by square cathodal current pulses. In our laboratory[23] we have shown that spontaneous depolarizations occurred after the release of voltage-clamp in short canine Purkinje fibers, and that the amplitude of these depolarizations correlated with the strength of the inward current flowing at the time of clamp release. These observations suggest that when the circumstances are appropriate, either single or repetitive depolarizations could arise spontaneously in the depolarized myocardium due to local action of calcium, catecholamines or other depolarizing stimuli. Future studies will undoubtedly focus on this and other aspects of calcium spikes. The new knowledge of these phenomena may bring us significantly closer toward understanding the mechanism of cardiac arrhythmias in patients with acute myocardial infarction and sudden cardiac death.

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LETTERS TO THE EDITOR

HEMODYNAMICS IN MYOCARDIAL INFARCTION

In their recent article Russell and co-workers[1] used both pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure as indicators of "left ventricular filling pressure." They feel that pulmonary arterial end-diastolic pressure "reliably reflected" left ventricular end-diastolic pressure[1] in acute myocardial infarction, a thesis that needs to be examined critically.[2]

Falicov et al.[3] and Bouchard et al.[4] have shown that pulmonary arterial end-diastolic pressure does not provide a reliable estimate of left ventricular end-diastolic pressure in the presence of chronic left ventricular disease. We have shown previously that pulmonary arterial end-diastolic pressure does not accurately reflect left ventricular end-diastolic pressure after acute myocardial infarction.[5] Since Russell et al. did not present tabulated data for each individual patient, it is difficult to know the precise range of differences between pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure in their patients with acute myocardial infarction. Figure 6 of their article showed a comparison of pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure and demonstrated that there was a considerable scatter of points. In their patients, the probable difference between pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure averaged 2.1 mm Hg with 1 standard deviation of 4.5 mm Hg and a P value of <0.001. In spite of this significant difference between the two pressures, if changes in left ventricular end-diastolic pressure were consistently and accurately reflected in pulmonary arterial end-diastolic pressure, then monitoring of the latter could be useful as an indicator of ventricular performance. Unfortunately, in many patients this does not occur. For example, Figure 6 from Russell's data[1] shows that in one patient left ventricular end-diastolic pressure and pulmonary arterial end-diastolic pressure were the same at 20 mm Hg, but at another time, when left ventricular end-diastolic pressure had increased to 30 mm Hg, pulmonary arterial end-diastolic pressure was unchanged at 20 mm Hg. In another patient both pressures were 18 mm Hg and when left ventricular end-diastolic pressure increased to 29 mm Hg, pulmonary arterial end-diastolic pressure fell to 16 mm Hg. Further, it has also been shown previously that various maneuvers may result in changes in the indirect estimates of left ventricular end-diastolic pressure (such as pulmonary arterial end-diastolic pressure) that are different not only in magnitude but also in direction from the changes seen in left ventricular end-diastolic pressure.[2,4]

The use to which the various measured pressures are to be put is clearly important. As we have pointed out previously,[2,5] if left ventricular filling pressures are monitored in patients with acute myocardial infarction, the following data are important: (1) left ventricular end-diastolic pressure to assess the performance characteristics of the left ventricle, and (2) mean left atrial pressure or mean pulmonary arterial wedge pressure or left ventricular diastolic pressure, pre *a* wave, to assess the pulmonary venous pressure and, thus, the risk to the patient that pulmonary edema will develop. Pulmonary arterial end-diastolic pressure gives a good indication of pulmonary venous pressure, but after myocardial infarction pulmonary arterial end-diastolic pressure may not be the same as mean pulmonary arterial wedge pressure because of some increase of pulmonary vascular resistance in many patients.[5] The difference between the two pressures may create a problem because it is easier to monitor pulmonary arterial end-diastolic pressure than mean pulmonary arterial wedge pressure over a period of several days. A Swan-Ganz catheter can be placed in the pulmonary artery and pulmonary arterial end-diastolic pressure and mean pulmonary arterial wedge pressure determined. If there is a discrepancy between the two pressures, the magnitude of the difference can be taken into account during monitoring of pulmonary arterial end-diastolic pressure.

In conclusion, in normal subjects the indirect estimates of left ventricular end-diastolic pressure (for example, pulmonary arterial end-diastolic pressure and mean pulmonary arterial pressure) are usually the same as left ventricular end-diastolic pressure, and "left ventricular filling pressure" may be used as a convenient term to refer to all of these indexes. However, in patients with left ventricular dysfunction the indirect estimates of left ventricular end-diastolic pressure are often not the same as left ventricular end-diastolic pressure and, further, may not accurately reflect changes in this pressure. Therefore, it would seem inappropriate to use the general term "left ventricular filling pressure" in patients with left ventricular dysfunction. It would be preferable to refer to the specific index measured instead of using "filling pressure" to cover all indexes.[2] Such a practice would be more accurate and would allow maximal utilization of data from studies performed by various investigators.

Acknowledgment

I thank Gary L. Grunkemeier, PhD, Department of Statistics, Oregon State University, Corvallis, Oregon for statistically analyzing data from Figure 6 of the paper by Russell et al.

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REPLY

We appreciate the interest expressed by Dr. Rahimtoola in our recent article[1] and the opportunity to clarify and amplify our position concerning the interpretation and clinical usefulness of pulmonary arterial end-diastolic pressure in acute myocardial infarction. We agree that each investigator and clinician should specify the variable measured in discussion of his results.[2] However, once clearly specified, it seems defensible and reasonable to employ some term such as left ventricular filling pressure[3] in reference to diastolic pressure events in the left ventricle to remind the clinician constantly that the Frank-Starling principle can be employed to manage acutely ill patients, including those with acute myocardial infarction.

We also agree that it is important to consider how the measured pressures are to be used. The clinician has become interested in measurement of left ventricular end-diastolic pressure, or a reasonably reliable reflection of it, particularly in the acutely ill patient, because (1) it provides information concerning the function of the left ventricle; (2) he may wish to alter it acutely, thus altering preload; and (3) it may provide information concerning the risk of pulmonary edema in the patient. As Rahimtoola indicates, there is little disagreement that, in the absence of increased pulmonary vascular resistance, pulmonary arterial end-diastolic pressure gives a good indication of pulmonary venous pressure and, thus, of the risk that pulmonary edema will develop.[4,5]

Debate persists concerning the validity of pulmonary arterial end-diastolic pressure as an indication of left ventricular end-diastolic pressure. In patients with chronic left ventricular disease the left ventricular end-diastolic pressure is greater than mean left atrial pressure as a result of atrial systole; in subjects with normal cardiovascular systems the left ventricular end-diastolic pressure and the mean left atrial pressure are approximately equal.[6] Knowledge of left ventricular end-diastolic pressure, or a reasonable reflection of it, provides important information regarding the performance characteristics of the left ventricle with respect to its preload or the forces within the wall of the ventricle at end-diastole. Although performance of the left ventricle is determined by its preload, its afterload, heart rate and intrinsic contractility, estimation of left ventricular preload is the focus of this discussion. Whereas preload is determined by left ventricular end-diastolic pressure, left ventricular end-diastolic volume (and the previous end-systolic volume), wall thickness and left ventricular geometry, the left ventricular end-diastolic pressure provides an acceptable estimate of preload. Control of left ventricular end-diastolic pressure allows a certain degree of regulation of left ventricular performance by the Starling mechanism.[7] Thus, left ventricular end-diastolic pressure, or a reasonable reflection of this measurement, is important to the clinician, particularly in the management of the acutely ill patient.

Although direct measurement of left ventricular pressure may be performed in patients with myocardial infarction,[8,9] hemodynamic monitoring for serial evaluation of the patient's course is hazardous because of arrhythmias and possible embolic phenomena.[10] Furthermore, Parmley et al.[11] found that measurement of left ventricular pressure provided little more information of clinical value than that obtained with the pulmonary arterial balloon catheter and measurement of cardiac output. Because of these considerations the search for a suitable substitute for left ventricular end-diastolic pressure has engendered much meritorious investigation.[4,5,12–19] Clearly, central venous pressure or mean right atrial pressure does not provide a meaningful substitute.[1,13,20,21] Although inflation of the balloon of the Swan-Ganz catheter gives a pulmonary wedge pressure that closely approximates mean left atrial pressure or a pre *a* wave left ventricular diastolic pressure, frequent inflation of the balloon leads to further floating of the catheter and the risk of pulmonary infarction. The balloon may inadvertently be left inflated or improperly deflated and the hazard of pulmonary infarction thus exists.

Pulmonary arterial end-diastolic pressure is frequently not precisely equal to left ventricular end-diastolic pressure in patients with acute myocardial infarction.[1,17] Nor are the two precisely equal in patients with myocardial disease or other forms of chronic left ventricular dysfunction,[4,14] particularly in patients with increased pulmonary vascular resistance,[4] or at heart rates faster than 125 beats/min or in the atrial fibrillation during short cycle lengths.[14] However, in our experience, pulmonary arterial end-diastolic pressure should not be measured "at the lowest point of its tracing" as suggested previously by Rahimtoola and associates.[17] The catheter with its tip in the pulmonary artery also lies partly in the right ventricle. The contraction of this chamber must frequently strike the catheter, producing motion artefact with resultant undershoot and doubtless falsification of the pressure as lower than physiologically present, if measured at the lowest point. We have observed commercial analog pressure read-out devices perform in this physiologically erroneous manner when attempting to read pulmonary arterial end-diastolic pressure. A more appropriate method, we believe, is to read the pressure on the plateau before the rise in the level of pulmonary arterial systolic pressure. One can judge this segment of pressure by visually averaging the fluctuations at this period on the pressure curve. Lest this be thought to be somewhat "individual," we have taught numerous physicians, nurses and technicians to read this pressure and a digital computer program has been written that seeks this plateau by finding the segment with least rapid pressure changes in this period of the cardiac cycle.

It remains to consider the use of pulmonary arterial pressure to assess the performance characteristics of the left ventricle. Rutherford et al.[16] demonstrated the separation of patients after myocardial infarction into those with and without a complicated course using mean pulmonary arterial pressure. Values for stroke volume index and pulmonary arterial oxygen saturation supported this classification. Rapaport and Scheinman[13] pointed out the value of pulmonary arterial end-diastolic pressure in management of the critically ill patient with shock or congestive heart failure. Rotman et al.[18] noted correlation of pulmonary arterial end-diastolic pressure with clinical classification, site of infarction, presence or absence of a third heart sound and rales and with hospital mortality. We have evaluated left ventricular performance on the basis of function curves relating cardiac index, stroke volume index or stroke work index to pulmonary arterial end-diastolic pressure as the latter is altered by rapid infusion of low molecular weight dextran with blood volume expansion.[22] We found that the ventricle does indeed follow a ventricular function curve using pulmonary arterial end-diastolic pressure as a reflection of left ventricular end-diastolic pressure. We have also found that the cardiac output after acute myocardial infarction can be increased and that the ventricle reaches a peak stroke index or cardiac index in the range of a pulmonary arterial end-diastolic pressure of 20 to 24 mm Hg although there is individual patient variation. The performance of the ventricle after acute myocardial infarction improves spontaneously in the first 2 or 3 days in the absence of any specific therapy as judged by these ventricular function curves.[22] Thus, the performance of the left ventricle can be serially monitored from pulmonary arterial end-diastolic pressure. However, if in the presence of left ventricular pump failure with cardiogenic shock or of pulmonary parenchymal disease with increased pulmonary vascular resistance, there is reason to suspect discrepancy between pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure or pulmonary capillary wedge pressure, one of these latter two pressures should be measured initially and the pulmonary arterial end-diastolic pressure calibrated for serial monitoring.

Let us summarize our thinking on the clinical usefulness

of pulmonary arterial end-diastolic pressure as a correlate and substitute for left ventricular end-diastolic pressure: (1) It may be hazardous to monitor serially left ventricular end-diastolic pressure or pulmonary capillary wedge pressure. (2) Pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure are similar in the absence of mitral valve disease, pulmonary parenchymal disease of moderate or marked severity, hypoxia, acidosis or alkalosis (which might alter pulmonary vascular tone) and heart rates exceeding 125 beats/min. (3) The method of measuring pulmonary arterial end-diastolic pressure is important. (4) The use of pulmonary arterial end-diastolic pressure is to provide a means to monitor the raising or lowering of left ventricular pre *a* wave and end-diastolic pressure without producing pulmonary edema. Experience suggests that this is feasible in the majority of patients with acute myocardial infarction even though a discrepancy may exist between pulmonary arterial end-diastolic pressure and left ventricular end-diastolic pressure. Furthermore, there is prognostic value in the pulmonary arterial end-diastolic pressure. (5) The term left ventricular filling pressure derives from earlier experimental studies relating mean left atrial pressure to left ventricular end-diastolic pressure. The term has come into common usage even though the implication that pulmonary arterial end-diastolic pressure, left ventricular end-diastolic pressure and left ventricular filling pressure are freely interchangeable is misleading. Nevertheless, the usage seems likely to continue.

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MEDICALLY UNCONTROLLABLE RECURRENT VENTRICULAR TACHYARRHYTHMIA IN ASSOCIATION WITH VENTRICULAR ANEURYSM

Clark and Russell[1] recently presented a case of recurrent ventricular tachycardia associated with ventricular aneurysm, controlled by medical treatment. Attention is drawn to a paper of Lull et al.,[2] in which surgical treatment was indicated in one case of ventricular tachycardia associated with myocardial sarcoidosis. Wasserman and Yules[3] indicated an association between intractable ventricular tachycardia and ventricular aneurysm, although some cases were reported previously.

In 1959, Couch[4] reported the first case of refractory ventricular tachycardia successfully treated by surgery with resection of a postinfarction ventricular aneurysm. Similar cases have since been reported.[5–8] Progressive congestive heart failure caused by tachyarrhythmia was considered by Lenegre et al.[9] the primary indication for surgery.

As a contribution to the subject, we describe three patients who underwent surgery for ventricular tachyarrhythmia associated with ventricular aneurysm not controlled by medical treatment.

Case 1: A 59 year old man with a history of two previous myocardial infarctions in 1965 and January 1971; the last was located on the posterior wall and produced mitral insufficiency. He was admitted into the coronary unit in September 1971, when his course was complicated by sinus tachycardia, left anterior hemiblock, right bundle branch block, atrioventricular (A–V) junctional rhythm at times, and paroxysmal ventricular tachycardia without signs of pulmonary congestion at rest.

Vigorous treatment with antiarrhythmic drugs proved a failure. Ten days later coronary arteriography and angiocardiography showed a left ventricular aneurysm of the posterior wall involving also the apex of the left ventricle, mitral insufficiency, enlarged left atrium without thrombus and severe coronary disease. Twenty-one days after admission, external plication of the aneurysm and valvuloplasty of the mitral valve were performed in addition to endarterectomy of the right coronary artery and right aortocoronary artery bypass. The insertion of the posterior papillary muscle of the mitral valve was found in the center of the aneurysmal sac, thus partially explaining the mitral insufficiency. The patient was discharged 11 days after operation and during the past 18 months has had no recurrence of ventricular tachycardia. A recent examination, June 1973, showed that he has sinus rhythm and is performing his habitual duties normally.

Case 2: A 59 year old man had an anteroseptal myocardial infarction in March 1971. He was admitted several times into the hospital with recurrent tachyarrhythmia without chest pain, dypsnea or heart failure at rest. In spite of vigorous antiarrhythmic drug treatment, only direct current electrical shock reverted the rhythm to normal tempo-

rarily. On January 18, 1972, angiocardiography and coronary arteriography revealed an anteroseptal aneurysm extending to the apex of the left ventricle and severe atherosclerosis of the three coronary vessels. Thirty-seven days after admission, resection of the left ventricular aneurysm, endarterectomy and saphenous vein bypass graft of the right coronary artery were performed. There was no recurrence of tachyarrhythmia for 1 year after surgery. Then the patient experienced two episodes of supraventricular tachycardia that were rapidly controlled by direct current electrical countershock. Since then there has been no recurrence of arrhythmia and the patient is leading a normal life.

Case 3: A 56 year old man with no previous history of angina was admitted to the coronary care unit on December 9, 1972 because of anteroseptal and posterior myocardial infarction. On admission a holosystolic precordial impulse was palpable. For 10 days the patient had isolated ventricular extrasystoles controlled by antiarrhythmic drugs. On the 26th day he manifested bigeminy followed by ventricular fibrillation, from which he was resuscitated by direct current electrical countershock. However, ventricular extrasystoles persisted, and at times bigeminy and on four occasions ventricular tachycardia occurred. Coronary arteriography and angiocardiography performed 32 days after hospital admission revealed a giant anterolateral aneurysm that covered more than 40 percent of the left ventriculogram, and severe diffuse coronary disease. In spite of vigorous medical treatment the patient had bouts of ventricular tachycardia. He was operated on as an emergency case, because of uncontrolled tachycardia, 39 days after myocardial infarction, and aneurysmectomy was performed. The patient was discharged on the 14th postoperative day with normal sinus rhythm. A recent examination in June 1973 indicated that he is leading a normal life.

In summary, medically uncontrollable tachyarrhythmia forced us to carry out surgical treatment in these three patients. In the first case plication of a posterior wall aneurysm, mitral valvuloplasty and right aortocoronary vein bypass combined with endarterectomy abolished the ventricular arrhythmia for 18 months. In Case 2, aneurysmectomy and right coronary bypass associated with right endarterectomy have prevented ventricular tachyarrhythmia for more than a year. Two episodes of supraventricular tachycardia were easily controlled by electrical shock, and there has been no recurrence in the last 6 months of observation. In Case 3 aneurysmectomy alone was performed. All three patients had advanced ischemic heart disease with diffuse coronary atherosclerosis. This diagnosis was confirmed by the finding that, in two patients, revascularization of the right coronary artery was possible only with combined endarterectomy.

Surgery was of definite benefit in all three cases after failure of medical treatment. We believe that medical therapy including cardioversion, cardiac pacing and antiarrhythmic drugs are useful to reverse the arrhythmic episodes but, in the presence of severe repetitive tachyarrythmia, surgery is indicated to obtain a permanent result.

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BOOK REVIEWS

CHANGING CONCEPTS IN CARDIOVASCULAR DISEASE edited by Henry I. Russek and Burton L. Zohman. Baltimore, Williams & Wilkins, 1972, 469 pages, $23.75

This volume contains the edited proceedings of the 1970 American College of Cardiology Saint Barnabas Symposium on New Frontiers in Cardiovascular Disease. The diverse scope of the book reflects the contributions of 56 authors on topics ranging from the ultrastructure of the myocardium, coronary artery disease, heart failure, cardiac arrhythmias, pulmonary heart disease, mechanical assistance and surgical excision, hypertension, exercise and periontogenic disease to human transplantation. Their discussions provide a summary of work in progress as well as classic work in various fields.

The major problems in this text are the lack of continuity between chapters and topics and the disproportionate amount of space alloted to certain material and the restriction of other subjects of equal importance (management of dissecting aneurysm of the aorta) to two pages. Many chapters are devoted to exercise and physical fitness, and there is a long, well illustrated, surgically oriented chapter on autologous tissue repair in mitral and aortic valvular disease (37 pages); only 5 pages are devoted to direct myocardial revascularization—a timely topic. Some chapters are especially well referenced (myocardial potassium balance, recent advances in the understanding of congestive heart failure, diagnosis and treatment of cardiomyopathy and physiologic basis of antianginal therapy), others not at all. Most are well written, but some provide inadequate discussion and analysis of a given subject matter and do not review controversial aspects.

The title of the book may be misleading to some, since the scope is of limited interest. Recent pharmacologic, electrophysiologic and surgical advances are omitted as are the newer noninvasive techniques, and the book provides only an incomplete review of some changing concepts in cardiovascular disease.

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CENTRAL HEMODYNAMICS AND GAS EXCHANGE (WITH EMPHASIS ON THE MEASUREMENT OF PULMONARY EXTRAVASCULAR WATER), edited by C. Giuntini, MD. Torino, Italy, Minerva Medica, 1971, 475 pages, $22.25

Although this text is a compilation of individual papers presented at a symposium on pulmonary water and water compartments, it is by no means a disjointed set of unrelated manuscripts, as is so often the case with the published records of scientific symposia. On the contrary, this book is a comprehensive overview of the present status of the theoretical and practical basis for the measurement of lung extravascular water, of the physiology of the pulmonary water compartments, that is, their osmotic and interstitial pressure and their extent, and the use of measurements in both man and animals during health and disease.

In the first section of the text, Zierler, Chinard et al. and Goreski et al. present theoretical reinforcement of present measurement techniques: The interested reader approaching this problem for the first time can quickly become acquainted with the development of these relatively sophisticated indicator-dilution techniques. Although much is a recapitulation of developments in this area over the past 20 years, new hypotheses, such as that of Zierler and Permutt on the relation between pulmonary blood flow and pulmonary extravascular water, are developed. The second section of the text tackles the difficult problems involving the physiology of the pulmonary water spaces and contains contributions by both West and Guyton. The latter's paper is an updated version of work defining interstitial pressures in tissue due to the presence of both solids and liquids and presents clearly what has always been a most difficult subject. The final section of the text features 10 contributions reporting techniques to measure lung water under a variety of circumstances in man. Thus, the effects of various factors on the pulmonary water compartments: (exercise in cardiac patients, acute hypoxia, myocardial infarction, early pulmonary edema, pulmonary embolism and the special pulmonary edema of high altitude) are all reported. It is apparent that much can be learned about the pathogenesis of various forms of pulmonary edema from meticulous measurements of the distribution of water throughout the lung by these techniques.

This volume ends appropriately with a proposal by Staub for a formalized nomenclature for the pulmonary "spaces" similar to the systems of symbols adapted by the respiratory and renal physiologists to make certain that investigators understand each other. The pertinence of such a system is underscored by the recent development of this hitherto specialized field of investigation into a much used approach in the study of human disease.

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AUDIOVISUAL SEMINARS IN PEDIATRICS. PEDIATRIC CARDIOLOGY, first edition, by Roland Schmidt, MD and George H. Khoury, MD. Philadelphia, WB Saunders, 1973, 83 pages, $75.00

The Pediatric Cardiology supplement of Audiovisual Seminars in Pediatrics is an innovative, although not particularly valuable, teaching aid. The "book" or unit consists of two taped cassettes (one half hour of recorded material on each side), four film strips corresponding to and coordinated with the tapes, and an accompanying 83 page pamphlet, much like an unabridged libretto, that reproduces the taped scenario word for word. The two subjects of discussion, cardiac examination of the child and rheumatic fever in children, are each 1 hour long when played; however, the material in the accompanying brochure can be read easily in less than 30 minutes. Included in the taped material are clinical examples of pathologic and innocent murmurs, but their reproduction on my own solid state cassette recorder left something to be desired. In all fairness, however, the authors recommend more sophisticated audio equipment for optimal results in playback. The user of this unit must also have access to a special film strip projector for the visual component of the learning process.

Because of the inherent time limitation in the method of presentation, the material is somewhat fragmentary and superficial. From an educational standpoint the text relates more to the requirements of a medical student rather than to the expanding horizons of the cardiologist. In general, I would say that the cost (in time and money) to benefit ratio of this pedagogic technique weighs heavily in favor of the former. Furthermore, without some drastic improvements, audiovisual seminars could hardly be expected to serve as a substitute for the patient or a standard textbook.

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REVIEWS IN CARDIOLOGY*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ANTICOAGULANTS

Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. Hirsh J, et al. **Postgrad Med** 55:211-7, Jan 74 (44 ref.)

AORTA

New microscopical approach to aortic intimal surface in experimental atherogenesis. Weber G. **Adv Exp Med Biol** 38:227-36, 1973 (28 ref.)

ARTERIAL OCCLUSIVE DISEASES

Proceedings: Myopathic-nephrotic-metabolic syndrome associated with massive acute arterial occlusions. Haimovici H. **J Cardiovasc Surg (Torino)** 14:589-600, Nov-Dec 73 (25 ref.)

ARTERIES

Role of the main arterial wall macromolecules in atherosclerosis. Velican C. **Rev Roum Med Intern** 10:441-56, 1973 (46 ref.)

ARTERIOSCLEROSIS

New microscopical approach to aortic intimal surface in experimental atherogenesis. Weber G. **Adv Exp Med Biol** 38:227-36, 1973 (28 ref.)

Role of the main arterial wall macromolecules in atherosclerosis. Velican C. **Rev Roum Med Intern** 10:441-56, 1973 (46 ref.)

BLOOD VESSELS

Environment of the blood-borne tumor embolus adherent to vessel wall. Warren BA. **J Med (Basel)** 4:150-77, 1973 (59 ref.)

CARDIAC OUTPUT

The catecholamines: reappraisal of their use for acute myocardial infarction and the low cardiac output syndromes. Kones RJ. **Crit Care Med** 1:203-20, Jul-Aug 73 (173 ref.)

CEREBROVASCULAR DISORDERS

Report of the joint committee for stroke facilities. IX. Strokes in children. 2. **Stroke** 4:1007-52, Nov-Dec 73 (237 ref.)

CORONARY DISEASE

Interactions between nutrition and heredity in coronary heart disease. Hatch FT. **Am J Clin Nutr** 27:80-90, Jan 74 (78 ref.)

Magnesium interrelationships in ischemic heart disease: a review. Seelig MS, et al. **Am J Clin Nutr** 27:59-79, Jan 74 (228 ref.)

EMBOLISM

Environment of the blood-borne tumor embolus adherent to vessel wall. Warren BA. **J Med (Basel)** 4:150-77, 1973 (59 ref.)

ENDOCARDITIS, BACTERIAL

Neurological manifestations of infective endocarditis: a review. Greenlee JE, et al. **Stroke** 4:958-63, Nov-Dec 73 (34 ref.)

HEART

Heart transplantation. The past, present problems and future. Mattila SP. **Ann Chir Gynaecol Fenn** 62:185-9, 1973 (15 ref.)

Determination of left ventricular size and shape. Sandler H, et al. **Circ Res** 40:1-8, Jan 74 (87 ref.)

HEART DEFECTS, CONGENITAL

Deep hypothermia in cardiovascular surgery. Rittenhouse EA, et al. **Ann Thorac Surg** 17:63-98, Jan 74 (142 ref.)

Systemic to pulmonary arterial shunts for patients with cyanotic congenital heart disease: current status. Litwin SB, et al. **Pediatr Radiol** 1:41-6, Mar 73 (24 ref.)

HEART DISEASES

Cardiac pathology--a look at the last five years. I. Robbins SL. **Hum Pathol** 5:9-24, Jan 74 (122 ref.)

HEART SEPTAL DEFECTS, ATRIAL

Familial incidence of atrial septal defect. A report of four siblings and review of the literature. Libshitz HI, et al. **Chest** 65:56-8, Jan 74 (18 ref.)

HEART SURGERY

Deep hypothermia in cardiovascular surgery. Rittenhouse EA, et al. **Ann Thorac Surg** 17:63-98, Jan 74 (142 ref.)

HYPERTENSION

Hypertensive emergencies. Koch-Weser J. **N Engl J Med** 290:211-4, 24 Jan 74 (14 ref.)

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MYOCARDIAL INFARCT

The catecholamines: reappraisal of their use for acute myocardial infarction and the low cardiac output syndromes. Kones RJ. **Crit Care Med** 1:203-20, Jul-Aug 73 (173 ref.)

Cardiac pathology--a look at the last five years. I. Robbins SL. **Hum Pathol** 5:9-24, Jan 74 (122 ref.)

MYOCARDIUM

Magnesium interrelationships in ischemic heart disease: a review. Seelig MS, et al. **Am J Clin Nutr** 27:59-79, Jan 74 (228 ref.)

Mitochondrial-cytosolic interactions in cardiac tissue: role of the malate-aspartate cycle in the removal of glycolytic NADH from the cytosol. Williamson JR, et al. **Symp Soc Exp Biol** 27:241-81, 1973 (165 ref.)

PULMONARY ARTERY

Systemic to pulmonary arterial shunts for patients with cyanotic congenital heart disease: current status. Litwin SB, et al. **Pediatr Radiol** 1:41-6, Mar 73 (24 ref.)

SHOCK

Shock. Differential diagnosis and immediate treatment. Campbell CD, et al. **Postgrad Med** 55:85-95, Jan 74 (38 ref.)

THROMBOEMBOLISM

Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. Hirsh J, et al. **Postgrad Med** 55:211-7, Jan 74 (44 ref.)

* Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue (Amer J Cardiol 28: 366–967, 1971).

Norms for Use in the Peer Review of Selected In-Hospital Cardiovascular Diagnoses

Developed by The American College of Cardiology
Bethesda, Maryland, February 1974*

FOREWORD

The ACC PSRO Sub-committee on Norms (defined as a numerical or statistical measure of usual observed performance) functioned within the following framework set forth by the ACC PSRO Committee:

"Realizing the importance of quality of patient care, we propose that the American College of Cardiology develop indices for use in reviewing the quality of cardiovascular practice. Furthermore, we propose that these indices be developed with regional input and that the indices be made available to all legitimate groups engaged in furthering the quality of patient care.

We also recognize that these American College of Cardiology indices may require regional modification and that certainly they will require review at intervals no longer than one year.

The development of these indices should not be interpreted as an indication of the American College of Cardiology's support of any program that would result in a constraint of the practice of cardiology or restriction of innovation."

The Sub-committee addressed itself to a hospital population and within this population identified and developed norms for diagnosis which comprise 75 percent of cardiovascular admissions. The list of special supporting procedures may appear all inclusive. This seemed proper because complications frequently modify the initially projected length of hospital stay, diagnostic and therapeutic approach. The norms as presented will be subject to periodic review.

Finally, the Sub-committee did not concern itself with criteria (defined as predetermined elements against which aspects of the quality of a medical service may be compared) nor with standards (defined as professionally developed expression of the range of acceptable variation from a norm or criteria).

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*Members of The Ad Hoc Committee appointed by College President H. J. C. Swan for the Development of Cardiovascular Norms are: Charles Fisch, MD, Chairman; Maxwell G. Berry, MD: Louis Gillespie, Jr., MD; R. Joe Noble, MD; Brendan Phibbs, MD; Arthur Selzer, MD; and Sylvan L. Weinberg, MD.

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DIAGNOSIS:
ARTERIOSCLEROTIC HEART DISEASE

I. *Indications for admission*
- A. Diagnostic: To establish new or additional diagnoses
- B. Therapeutic: Initial treatment—unresponsive to outpatient regimens
- C. Complications: New symptoms or findings
  1. Unstable angina
  2. Myocardial infarction (See under myocardial infarction)
  3. Congestive failure (See under congestive failure)
  4. Arrhythmias
  5. Involvement of other organ systems

II. *Criteria for diagnosis*
- A. History
  1. No symptoms may be present
  2. Symptoms
     - a. Pain (chest, either arm, neck, throat, upper abdomen); pain equivalents (pressure, burning, tingling, nausea)
     - b. Shortness of breath
     - c. Weakness
     - d. Cough
     - e. Swelling (feet, ankles, legs)
     - f. Cyanosis (bluish discoloration of lips or nailbeds)
     - g. Palpitation, syncope
     - h. Syncope and/or seizures
- B. Physical findings
  1. Enlargement of heart
  2. Fluid retention
     - a. Congestion in lungs
     - b. Distention of neck vein
     - c. Engorgement of liver or spleen
     - d. Edema of lower extremities
     - e. Ascites
     - f. Pleural effusion
     - g. Pericardial effusion
  3. Auscultatory abnormalities
     - a. Heart murmurs
     - b. Gallop sounds (S_2–S_3)
     - c. Pericardial friction rub
  4. Abnormalities of heart rate, rhythm and blood pressure
  5. Heart may be normal on physical examination
  6. Pulsus alternans
- C. Laboratory tests
  1. Usual
     - a. Chest X-ray
     - b. Electrocardiogram
     - c. Complete blood count
     - d. Urinalysis
     - e. Sedimentation rate
     - f. Blood urea nitrogen
     - g. Creatinine
     - h. Serum electrolytes
     - i. Blood sugar
     - j. Enzymes
  2. Occasional
     - a. Blood gases
     - b. Lipids
     - c. Prothrombin time
     - d. Uric acid
     - e. Appropriate as indicated to define further cardiovascular system or other organ systems
- D. Special diagnostic procedures
  1. Cardiac fluoroscopy
  2. Central venous pressure
  3. Vectorcardiogram
  4. Phonocardiogram
  5. Apex cardiogram
  6. Coronary arteriogram
  7. Cardiac catheterization
  8. Echocardiogram
  9. Stress testing
  10. Pericardiocentesis
  11. Pulmonary arteriogram
  12. Lung scan

III. *Basic medical management*
- A. Special care unit
  1. Coronary—intensive care
  2. Respiratory care
  3. Convalescent monitoring unit
- B. Therapy, medical
  1. Usual
     - a. Drug therapy
     - b. Intravenous fluids
     - c. Oxygen therapy
  2. Occasional
     - a. Pacemaker
     - b. Cardioversion
     - c. Defibrillation
- C. Therapy, surgical
  1. Pacemakers
  2. Heart surgery
  3. Intraaortic balloon assist device
  4. Embolectomy
  5. Cardiac transplantation

IV. *New or additional diagnosis (e.g., complications)*
- A. Renal failure
- B. Hepatic failure
- C. Pneumonia
- D. Systemic emboli
- E. Pulmonary emboli
- F. Endocarditis
- G. Stroke
- H. Diabetic acidosis
- I. Sepsis
- J. Shock
- K. Congestive heart failure
- L. Pericarditis
- M. Cardiac rupture
- N. Arrhythmias
- O. Myocardial rupture
- P. Myocardial aneurysm
- Q. Papillary muscle dysfunction
- R. Valvular involvement
- S. Psychosis
- T. Thrombophlebitis

V. *Consultations*
- A. Internal medicine/cardiology
- B. As required by #IV above
- C. Surgical

VI. *Length of hospital stay (with applicable modifiers)*
Range 0 to indefinite as may be modified by #IV above

VII. *Factors modifying standard care*
- A. Renal failure
- B. Hepatic failure
- C. Pneumonia
- D. Systemic emboli
- E. Pulmonary emboli
- F. Endocarditis
- G. Stroke
- H. Diabetic acidosis
- I. Sepsis
- J. Shock
- K. Congestive heart failure
- L. Pericarditis
- M. Cardiac rupture
- N. Arrhythmias
- O. Myocardial rupture
- P. Myocardial aneurysm
- Q. Papillary muscle dysfunction
- R. Valvular involvement
- S. Psychosis
- T. Thrombophlebitis

DIAGNOSIS:
MYOCARDIAL INFARCTION, UNCOMPLICATED

I. *Indications for admission*
- A. No symptoms may be present
- B. Symptoms
  1. Pain (chest, either arm, neck, throat, upper abdomen); pain equivalents (pressure, burning, tingling, nausea)
  2. Shortness of breath
  3. Weakness

II. *Criteria for diagnosis*
- A. History
  1. No symptoms may be present
  2. Symptoms
     a. Pain (chest, arm, neck, throat, upper abdomen); pain equivalents (pressure, burning, tingling, nausea)
     b. Shortness of breath
     c. Weakness
     d. Cough
     e. Swelling (feet, ankles, legs)
     f. Cyanosis
     g. Palpitations, syncope
     h. Syncope and/or seizures
- B. *Physical findings*
  1. Enlargement of heart
  2. Fluid retention
     a. Congestion in lungs
     b. Distention of neck vein
     c. Engorgement of liver or spleen
     d. Edema of lower extremities
     e. Ascites
     f. Pleural effusion
     g. Pericardial effusion
  3. Auscultatory abnormalities
     a. Heart murmurs
     b. Gallop sounds (S_2–S_3)
     c. Pericardial friction rub
  4. Abnormalities of heart rate, rhythm and blood pressure
  5. Heart may be normal on physical examination
  6. Pulsus alternans
- C. *Laboratory tests*
  1. Usual
     a. Chest X-ray
     b. Electrocardiogram
     c. Complete blood count
     d. Urinalysis
     e. Sedimentation rate
     f. Blood urea nitrogen
     g. Creatinine
     h. Serum electrolytes
     i. Blood sugar
     j. Enzymes
  2. Occasional
     a. Blood gases
     b. Lipids
     c. Prothrombin time
     d. Uric acid
     e. Appropriate as indicated to define further cardiovascular systems or other organ systems
- D. *Special diagnostic procedures*
  1. Cardiac fluoroscopy
  2. Central venous pressure
  3. Vectorcardiogram
  4. Phonocardiogram
  5. Apex cardiogram
  6. Coronary arteriogram
  7. Cardiac catheterization
  8. Echocardiogram
  9. Stress testing
  10. Pericardiocentesis
  11. Pulmonary arteriogram
  12. Lung scan

III. *Basic medical management*
- A. Special care unit
  1. Coronary—intensive care
  2. Respiratory care
  3. Convalescent monitoring unit
- B. Therapy, medical
  1. Bed rest
  2. Usual additions
     a. Drug therapy
     b. Intravenous fluids
     c. Oxygen therapy
  3. Occasional additions
     a. Pacemaker
     b. Cardioversion
     c. Defibrillation
- C. Therapy, surgical
  None

IV. *New or additional diagnosis (e.g., complications)*
- A. Renal failure
- B. Hepatic failure

C. Pneumonia
D. Systemic emboli
E. Pulmonary emboli
F. Endocarditis
G. Stroke
H. Diabetic acidosis
I. Sepsis
J. Shock
K. Congestive heart failure
L. Pericarditis
M. Cardiac rupture
N. Arrhythmias
O. Myocardial rupture
P. Myocardial aneurysm
Q. Papillary muscle dysfunction
R. Valvular involvement
S. Psychosis
T. Thrombophlebitis

V. *Consultations*
None may be required

VI. *Length of hospital stay (with applicable modifiers)*
A. Coronary care unit or other specialized units: range 0–7 days
B. Intermediate care unit or monitoring facility when available, for duration of hospital stay: range 14–17 days
C. Total hospital stay: range 14–24 days

VII. *Factors modifying standard care*
A. Renal failure
B. Hepatic failure
C. Pneumonia
D. Systemic emboli
E. Pulmonary emboli
F. Endocarditis
G. Stroke
H. Diabetic acidosis
I. Sepsis
J. Shock
K. Congestive heart failure
L. Pericarditis
M. Cardiac rupture
N. Arrhythmias
O. Myocardial rupture
P. Myocardial aneurysm
Q. Papillary muscle dysfunction
R. Valvular involvement
S. Psychosis
T. Thrombophlebitis

DIAGNOSIS:
SYSTEMIC ARTERIAL HYPERTENSION (BASIC)

I. *Indications for admission*
A. Sustained elevated diastolic blood pressure with clinical suspicion of secondary cause of hypertension
B. Failure to respond to antihypertensive therapy

II. *Criteria for diagnosis*
A. History
Sustained elevation of diastolic blood pressure
B. Physical findings
Sustained elevation of diastolic blood pressure; no other findings necessary
C. Laboratory tests
1. Usual
a. Chest X-ray
b. Complete blood count
c. Urinalysis
d. Blood urea nitrogen
e. Creatinine
f. Serum electrolytes
g. Blood sugar
h. Electrocardiogram
2. Occasional
a. Urine culture
b. Urinary VMA or catecholamines
c. Plasma or urinary steroids
d. Creatinine clearance
e. Urinary aldosterone
f. Lipoprotein electrophoresis
g. Serum triglycerides
h. Glucose tolerance test
D. Special diagnostic procedures
1. Excretory urogram
2. Renal arteriogram
3. Renal vein and/or peripheral venous renin assays
4. Cystoscopy with retrograde pyelography and/or separate renal function studies

III. *Basic medical management*
A. Special care unit
None needed
B. Therapy, medical
Drug therapy
C. Therapy, surgical
Renal, adrenal or vascular surgery

IV. *New or additional diagnosis (e.g., complications)*
A. Congestive heart failure
B. Renal failure (azotemia)
C. Hypertensive encephalopathy
D. Subarachnoid or intracerebral hemorrhage
E. Difficulty in regulating antihypertensive drugs
F. Surgery
G. Involvement of other organ systems
H. Epistaxis

V. *Consultations*
A. Internal medicine/cardiology
B. Urology
C. Surgery
D. As required by # IV

VI. *Length of hospital stay (with applicable modifiers)*
Range 1–28 days

VII. *Factors modifying standard care*
A. Congestive heart failure
B. Renal failure (azotemia)
C. Hypertensive encephalopathy
D. Subarachnoid or intracerebral hemorrhage
E. Difficulty in regulating antihypertensive drugs
F. Surgery
G. Involvement of other organ systems
H. Epistaxis

DIAGNOSIS:
SYSTEMIC ARTERIAL HYPERTENSION
(ACUTE ONSET IN ADULT)

I. *Indications for admission*
  A. Sustained elevated diastolic blood pressure
  B. Clinical suspicion of secondary cause of hypertension
II. *Criteria for diagnosis*
  A. History
    Sustained elevation of diastolic blood pressure
  B. Physical findings
    1. Sustained elevation of diastolic blood pressure
    2. no other findings necessary
  C. Laboratory tests
    1. Usual
      a. Chest X-ray film
      b. Complete blood count
      c. Urinalysis
      d. Blood urea nitrogen
      e. Creatinine
      f. Serum electrolytes
      g. Blood sugar
      h. Electrocardiogram
      i. Uric acid
      j. Serum cholesterol
    2. Occasional
      a. Urine culture
      b. Urinary VMA or catecholamines
      c. Plasma or urinary steroids
      d. Creatinine clearance
      e. Urinary aldosterone
      f. Lipoprotein electrophoresis
      g. Serum triglycerides
      h. Glucose tolerance test
  D. Special diagnostic procedures
    1. Excretory urogram
    2. Renal arteriogram
    3. Renal vein and/or peripheral venous renin assays
    4. Cystoscopy with retrograde pyelography and/or separate renal function studies
III. *Basic medical management*
  A. Special care unit
    1. Possible intensive care unit—i.e., acute congestive heart failure
    2. Possible renal dialysis unit—i.e., acute or chronic renal failure requiring dialysis
  B. Therapy, medical
    1. Usual
      Drug therapy
    2. Occasional
      Special dietary restrictions
  C. Surgical
    Renal, adrenal or vascular surgery
IV. *New or additional diagnosis (e.g., complications)*
  A. Congestive heart failure
  B. Renal failure (azotemia)
  C. Hypertensive encephalopathy
  D. Subarachnoid or intracerebral hemorrhage
  E. Difficulty in regulating antihypertensive drugs
  F. Surgery
  G. Involvement of other organ systems
  H. Epistaxis
V. *Consultations*
  A. Internal medicine/cardiology
  B. Urology
  C. Surgery
  D. Renal
  E. As required by #IV
VI. *Length of hospital stay (with applicable modifiers)*
  Range 1–28 days
VII. *Factors modifying standard care*
  A. Congestive heart failure
  B. Renal failure (azotemia)
  C. Hypertensive encephalopathy
  D. Subarachnoid or intracerebral hemorrhage
  E. Difficulty in regulating antihypertensive drugs
  F. Surgery
  G. Involvement of other organ systems
  H. Epistaxis

DIAGNOSIS:
SYSTEMIC ARTERIAL HYPERTENSION
WITH ENCEPHALOPATHY

I. *Indications for admission*
  A. Elevated diastolic blood pressure with neurologic or sensorium abnormalities
II. *Criteria for diagnosis*
  A. History
    1. Elevation of diastolic blood pressure
    2. Possible abnormality of sensorium
  B. Physical findings
    1. Elevation of diastolic blood pressure
    2. Possible neurologic abnormalities
    3. Fundoscopy noted: positive or negative findings
  C. Laboratory tests
    1. Usual
      a. Chest X-ray film
      b. Complete blood count
      c. Urinalysis
      d. Blood urea nitrogen
      e. Creatinine
      f. Serum electrolytes
      g. Blood sugar
      h. Electrocardiogram
      i. Uric acid
      j. Serum cholesterol
    2. Occasional
      a. Urine culture
      b. Urinary VMA or catecholamines
      c. Plasma or urinary steroids
      d. Creatinine clearance
      e. Urinary aldosterone
      f. Lipoprotein electrophoresis
      g. Serum triglycerides
      h. Glucose tolerance test
      i. Spinal fluid examination
  D. Special diagnostic procedures
    1. Usual

a. Excretory urogram
b. Renal arteriogram
c. Renal vein and/or peripheral venous renin assays
d. Cystoscopy with retrograde pyelography and/or separate renal function studies

2. Occasional
a. Electroencephalogram
b. Brain scan
c. Cerebral arteriography

III. *Basic medical management*
A. Special care unit
Possible intensive care unit
B. Therapy, medical
1. Usual
Drug therapy
2. Occasional
Special dietary restrictions
C. Therapy, surgical
Renal, adrenal or vascular surgery

IV. *New or additional diagnosis (e.g., complications)*
A. Congestive heart failure
B. Renal failure (azotemia)
C. Hypertensive encephalopathy
D. Subarachnoid or intracerebral hemorrhage
E. Difficulty in regulating antihypertensive drugs
F. Surgery
G. Involvement of other organ systems
H. Epistaxis

V. *Consultations*
A. Internal medicine/cardiology
B. Surgery
C. Urology
D. As required by #IV

VI. *Length of hospital stay (with applicable modifiers)*
Range 5–20 days

VII. *Factors modifying standard care*
A. Congestive heart failure
B. Renal failure (azotemia)
C. Hypertensive encephalopathy
D. Subarachnoid or intracerebral hemorrhage
E. Difficulty in regulating antihypertensive drugs
F. Surgery
G. Involvement of other organ systems
H. Epistaxis

DIAGNOSIS: CONGESTIVE HEART FAILURE

I. *Indications for admission*
A. Diagnostic admission, i.e., to establish etiology, functional significance of lesion, anatomical or physiological derangement
B. New diagnosis, to establish response to therapy
C. Unresponsive to outpatient management
D. Complications

II. *Criteria for diagnosis*
A. History
1. May be asymptomatic
2. Usually: dyspnea, fatigability, effort intolerance, edema

B. Physical findings
1. May be normal
2. S_3 or S_4 heart sounds
3. Pulmonary rales
4. Cardiac murmurs
5. Abdominal organomegaly
6. Edema
7. Venous hypertension

C. Laboratory tests
1. Usual
a. Chest X-ray film
b. Electrocardiogram
c. Blood urea nitrogen or creatinine
d. Hemoglobin or hematocrit
e. Urinalysis
f. Serum electrolytes
g. Uric acid
2. Occasional
a. Cardiac enzymes
b. Creatinine clearance or special tests for renal function
c. Thyroid function tests
d. Hepatic function tests

D. Special diagnostic procedures
1. Cardiac fluoroscopy
2. Echocardiogram
3. Graphic recordings of phonocardiogram, apex cardiogram, arterial pulse, venous pulse
4. Cardiac catheterization
5. Venous pressure
6. Stress testing
7. Lung scan
8. Pulmonary angiogram

III. *Basic medical management*
A. Special care unit
1. None
2. Intensive care
B. Therapy, medical
1. Usual
a. Sodium restriction
b. Drugs
2. Occasional
a. Thoracentesis
C. Therapy, surgical
1. Usually none
2. May require palliative cardiac surgery

IV. *New or additional diagnosis (e.g., complications)*
A. Pulmonary embolization
B. Myocardial infarction
C. Pneumonia
D. Renal insufficiency and/or electrolyte imbalance
E. Arrhythmia
F. Valvular disease

V. *Consultations*
A. None
B. Internal medicine/cardiology
C. Cardiovascular surgery

VI. *Length of hospital stay (with applicable modifiers)*
Range 1 day–indefinite

VII. *Factors modifying standard care*
- A. Pulmonary embolization
- B. Myocardial infarction
- C. Pneumonia
- D. Renal insufficiency and/or electrolyte imbalance
- E. Arrhythmia
- F. Valvular disease

DIAGNOSIS:
ATRIAL FIBRILLATION

I. *Indications for admission*
- A. Newly discovered—for possible conversion to sinus rhythm
- B. Rapid rate requiring prompt slowing
- C. Failure to respond to ordinary therapy
- D. Unusual etiology suspected (e.g., thyrotoxicosis, anemia)
- E. Severe hypotension, shock
- F. Heart failure
- G. Chest pain (angina, impending infarction)
- H. Syncope
- I. Embolization

II. *Criteria for diagnosis*
- A. History
  Symptomatology referable to:
  1. The underlying disorder
  2. Atrial fibrillation per se (e.g., palpitations)
  3. Complications of the rapid rate (failure, coronary insufficiency)
  4. None
- B. Physical findings
  1. Cardiovascular findings other than atrial fibrillation (that of underlying disease)
  2. Apical and radial rates—pulse deficit
  3. Absence of *A* waves
  4. Irregular apical and radial pulse
- C. Laboratory tests
  1. Usual
     a. Electrocardiogram
     b. Chest X-ray
     c. Other tests necessary to diagnose underlying etiology
  2. Occasional
     a. Cardiac fluoroscopy
     b. Echocardiogram
- D. Special diagnostic procedures
  1. None for atrial fibrillation, per se
  2. Intracardiac electrocardiogram (occasionally)

III. *Basic medical management*
- A. Special care unit
  May be used if complicated by shock, chest pain, heart failure
- B. Therapy, medical
  1. Usual
     Drug therapy
  2. Occasional
     Cardioversion (electrical)
- C. Therapy, surgical
  None

IV. *New or additional diagnosis (e.g., complications)*
- A. Shock
- B. Chest pain (angina → infarction)
- C. Congestive failure
- D. Embolization

V. *Consultations*
Internal medicine/cardiology

VI. *Length of hospital stay (with applicable modifiers)*
Range 1–21 days

VII. *Factors modifying standard care*
Complications as indicated in #IV
- A. Unusual etiology
- B. Shock
- C. Chest pain (angina → infarction)
- D. Congestive failure
- E. Embolization

DIAGNOSIS:
VALVULAR HEART DISEASE (MITRAL)

I. *Indications for admission*
- A. Presence of asymptomatic mitral disease (for study)
- B. Heart failure
- C. Complications

II. *Criteria for diagnosis*
- A. History
  1. No symptoms
  2. Dyspnea
  3. Palpitations
  4. Swelling of ankles
  5. Hemoptysis
- B. Physical findings
  1. Murmurs of mitral valve disease
  2. Opening snap (mitral stenosis)
  3. Signs of cardiac failure
  4. Actuated S_1 (mitral stenosis)
  5. Parasternal lift
- C. Laboratory tests
  1. Usual
     a. Electrocardiogram
     b. Chest X-ray
  2. Occasional
     Echocardiogram
- D. Special diagnostic procedures
  1. Cardiac catheterization
  2. Angiocardiography
  3. Graphic recordings
  4. Coronary arteriography (when clinically indicated)

III. *Basic medical management*
- A. Special care unit
  1. Severe cardiac failure
  2. Tachyarrhythmia
  3. Pulmonary embolus
- B. Therapy, medical
  Drug therapy
- C. Therapy, surgical
  1. Mitral valvotomy
  2. Valvuloplasty
  3. Valve replacement

IV. *New or additional diagnosis (e.g., complications)*
- A. Arrhythmias—especially atrial fibrillation
- B. Bacterial endocarditis
- C. Systemic embolization
- D. Severe hemoptysis
- E. Pulmonary embolism
- F. Pulmonary hypertension
- G. Heart failure

V. *Consultations*
1. Internal medicine/cardiology
2. Cardiovascular surgeon
3. As may be required by #4.

VI. *Length of hospital stay (with applicable modifiers)*
Range 1–24 days

VII. *Factors modifying standard care*
- A. Arrhythmias, especially atrial fibrillation
- B. Bacterial endocarditis
- C. Systemic embolization
- D. Severe hemoptysis
- E. Pulmonary embolism
- F. Pulmonary hypertension
- G. Heart failure

DIAGNOSIS:
VALVULAR HEART DISEASE (AORTIC)

I. *Indications for admission*
- A. Presence of asymptomatic severe aortic disease (for study)
- B. Heart failure
- C. Complications
- D. Chest pain
- E. Dizziness or syncope

II. *Criteria for diagnosis*
- A. History
  1. No symptoms
  2. Dyspnea
  3. Chest pain
  4. "Fainting"
  5. Dizziness
  6. Swelling of ankles
- B. Physical findings
  1. Characteristic murmurs of aortic valve disease
  2. Changes in character of arterial pulse
  3. Evidence of cardiac failure may be present
  4. Aortic thrill
- C. Laboratory tests
  1. Usual
     a. Electrocardiogram
     b. Chest X-ray
  2. Occasional
     a. Echocardiogram
- D. Special diagnostic procedures
  1. Cardiac catheterization
  2. Angiocardiography
  3. Graphic recordings
  4. Coronary arteriography (when clinically indicated)

III. *Basic medical management*
- A. Special care unit
  Aortic stenosis with cardiac failure may require management in intensive care units
- B. Therapy, medical
  Drugs
- C. Therapy, surgical
  Aortic valve surgery (usually valve replacement)

IV. *New or additional diagnosis (e.g., complications)*
- A. Arrhythmias
- B. Bacterial endocarditis
- C. Thromboembolism
- D. Postsurgical complications
- E. Progressive angina or myocardial infarction
- F. Heart failure

V. *Consultations*
- A. Internal medicine/cardiology
- B. Cardiovascular surgeon
- C. As may be required by #IV

VI. *Length of hospital stay (with applicable modifiers)*
Range 1–24 days

VII. *Factors modifying standard care*
- A. Arrhythmias
- B. Bacterial endocarditis
- C. Thromboembolism
- D. Postsurgical complications
- E. Progressive angina or myocardial infarction
- F. Heart failure

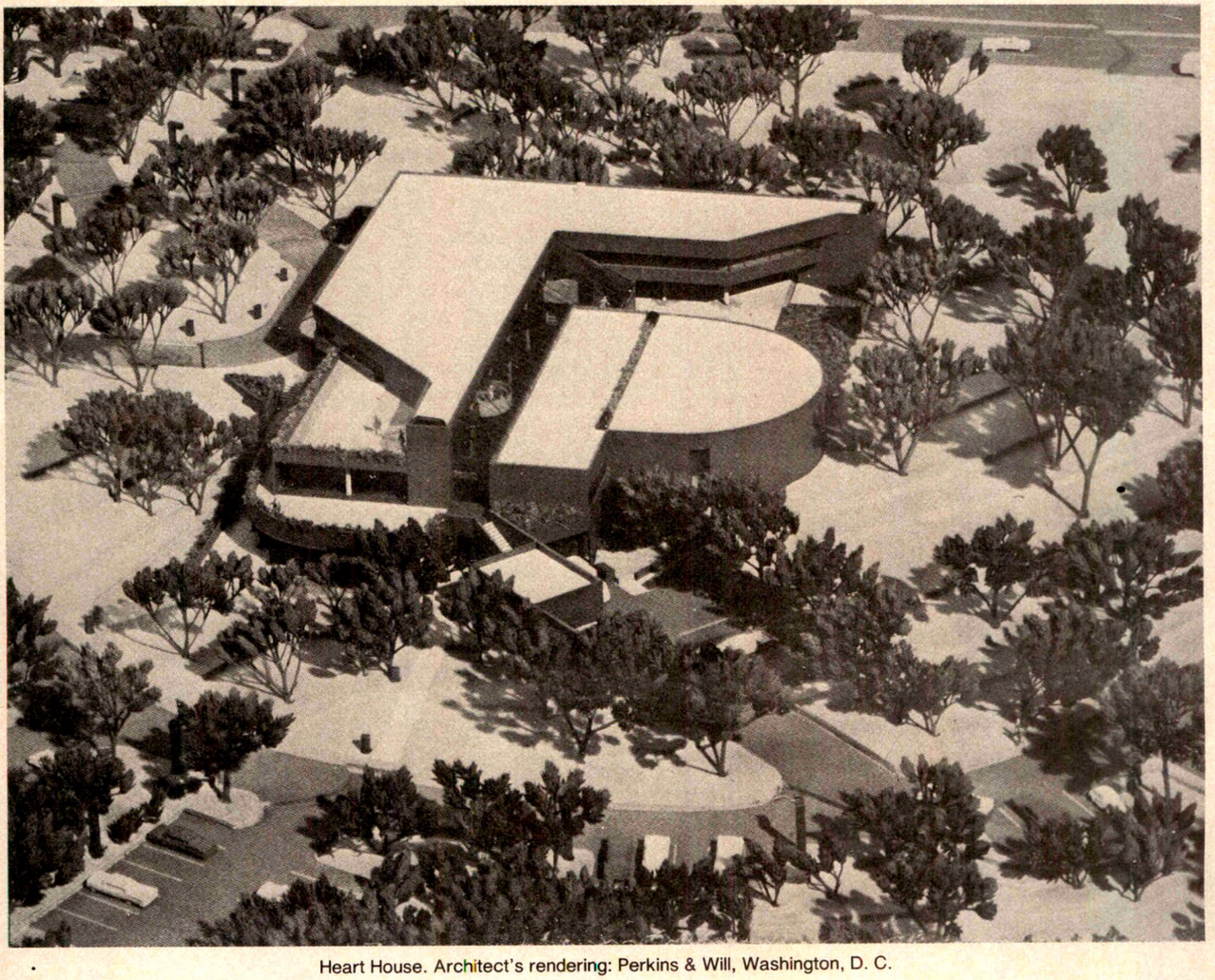
President's Page

In my last letter I indicated that future letters would be devoted to problems of personal concern to the Members of the College and cardiologists in general. Thus, I should like to discuss in some detail Heart House, which is to be built in Bethesda, Maryland.

My first reaction several years ago to Heart House was negative. After all, Bethesda is a long way from Houston. As Chairman of a Department of Medicine, I thought that we did a pretty good job in helping to meet the continuing education needs of physicians. In addition, I was already committed to about as much "charity" as I could afford and we were in the midst of a large local fund raising campaign in Houston. Finally, it looked as though the present recession (despite what the Administration wishes to call it) was inevitable. Construction costs were too high and were rising constantly. It therefore seemed foolhardy to consider trying to raise $5 million for a building and equipment and another $2 million for an endowment.

Nevertheless, I listened to Dwight Harken, Bill Martz, Grey Dimond, Forrest Adams, Don Dupler, Sam Fox, George Griffith, Bob Oblath, Bill Likoff, Ken Kohlstaedt, Bill Sodeman, Jeremy Swan, Suzanne Knoebel, Charles Fisch, Bill Roberts, Simon Dack and many others talk about the advantages; finally, I reexamined my thinking. I became convinced that Heart House will be one of the most important accomplishments that the American College of Cardiology has ever undertaken; furthermore it can be one of the most important things that will happen to American medicine during the present decade.

Heart House is not to be just an office building to house the headquarters and administrative functions of the Col-



Heart House. Architect's rendering: Perkins & Will, Washington, D. C.

lege. If that was all we needed, with construction costs as they are, it would be more economical to rent office space in Bethesda. But Heart House is to be a Learning Center. It is to be the hub of cardiovascular continuing education for American medicine.

There will be a Classroom for 60 students with comfortable seats equipped with individual stethophones, monitors for easy viewing of physiologic data and other parameters, and terminals for student response systems. The seats will be located so as to afford easy viewing of patients and other demonstrations and easy informal communication with the instructor. The classroom will be able to accommodate up to 120 for more formal presentations. There will be a Library with current journals and texts and ready access to the National Library of Medicine and the facilities of the proposed Lister Hill Center for Medical Communication. In fact, Heart House might be considered an outreach or an entrance to these institutions as well as the National Institutes of Health and the Federal Medical School to be constructed shortly on the campus of the U. S. Naval Hospital at Bethesda. Heart House will be within 1 mile of these facilities. There will be individual study carrels where the student can study, at his own pace, prepared material on all aspects of cardiology. In addition, there will be six conference rooms that will permit informal workshops or seminars.

Heart House will have the capabilities for closed-circuit television and planning and producing video teaching aids, self-assessment examinations, and the like. It will become the center for activities to identify what is important for the practicing cardiologist to learn, how he can best learn and how he can retain and use what he learns. It will also house the College headquarters.

It is obvious that if the Learning Center can accommodate only 120 students at most, and if it is located in Bethesda, it will take many years to accommodate all of the members and friends of the College. It might appear, therefore, to offer little to the members in Texas, Iowa, Washington State and Florida.

But the Learning Center is just that. It is a Center where the major emphasis is to be on learning. It is planned that we will have programs for members and other physicians to help with their teaching as well as learning techniques. The thoughtful physician knows that the best way to learn is to teach. The Center will develop techniques for programs that can be presented in Texas, Iowa, Washington State and Florida. Heart House will be a Learning Center for catalyzing learning of cardiology throughout the country.

One might ask, Is this function not being carried out by the medical schools? The answer is a guarded "Yes, but" . . . the medical schools have limited facilities . . . they have limited personnel compared to the membership of the American College of Cardiology. Actually, the College can claim faculty members from 114 medical schools. More importantly the College has enormous input from practicing cardiologists and cardiovascular surgeons, and other specialists. Thus, the program, the learning, will be more relevant to patient care. But the College will continue to conduct its 2 to 5 day programs throughout the country in conjunction with medical schools and teaching centers as in the past. As a result of what has been presented at the Learning Center, these programs will be better.

Being located near Washington and the Capitol, Heart House will have a profound effect on national planning for health, not just for cardiology, but for the whole field of medicine. It will become a home for the successful Bethesda conferences that have been conducted in the past by the College and have had a profound effect on a number of aspects of medicine.

For these and other reasons I became an enthusiastic supporter of Heart House. I pledge that during this year, while I am President, we will raise the necessary money so as to break ground, and we *will* break ground for Heart House in Bethesda. But in order to accomplish this, I need your help.

Under the leadership of Dwight Harken and his Campaign Funds Committee, as of February 28, 1974, $1,710,434 has been pledged. There are 256 Founders and 60 Benefactors. A Founder has pledged $1,000 over 3 years or less and a Benefactor, $3,000. This represents only a dollar a day or $3 a day for 3 years. That is a small price to pay.

But we have a long way to go. It is imperative that we get 1,000 more Founders or Benefactors. If you are not already one, won't you become one? Or if you are already a Founder, won't you move up and become a Benefactor?

In addition, we are seeking 400 members for the "Order of William Harvey." These members will agree, in addition to their present contributions, to raise $4,000 from patients, other fellows, other members, industry, foundations and other sources. We are preparing a special packet of information for those who agree to join the "Order of William Harvey" which will include pledge cards, literature and a small plaque describing the program for the office waiting room. The members of the "Order of William Harvey" will be recognized on a special plaque in Heart House and by certificates suitable for framing. They will have a special name badge and be invited to a special reception at the next ACC meeting in Houston. They will indeed be a select group in the life of the College for collectively they will have raised over $2 million.

Fifty thousand dollars was raised by a small group of members who worked very diligently at the last annual meeting of the ACC in New York. The efforts of this group served to spawn the idea of organizing the "Order of William Harvey." As a result of efforts in New York, the following, along with other "workers," are designated charter members of the "Order of William Harvey":

William B. Abrams, MD, New Jersey
Louis F. Bishop, MD, New York
Eliot Corday, MD, California
Simon Dack, MD, New York
E. Grey Dimond, MD, Missouri
Leonard S. Dreifus, MD, Pennsylvania
Donald A. Dupler, MD, Pennsylvania
George C. Griffith, MD, California
Rolf M. Gunnar, MD, Illinois
Dwight E. Harken, MD, Massachusetts
Suzanne B. Knoebel, MD, Indiana
Kenneth G. Kohlstaedt, MD, Indiana
Seymoure Krause, MD, Pennsylvania
William Likoff, MD, Pennsylvania
Henry D. McIntosh, MD, Texas
Oscar Magidson, MD, California
B. L. Martz, MD, Missouri
Robert W. Oblath, MD, California
Henry I. Russek, MD, New York
H. J. C. Swan, MD, California
Sylvan L. Weinberg, MD, Ohio

Won't you become a Founder or a Benefactor as well as a member of the "Order of William Harvey?" Please fill in

the attached pledge card and mail it to the College Office. It should be obvious that we would welcome larger contributions. For example, one may have a chair in the Classroom named in honor of oneself, a respected colleague, teacher or loved one for $6,300; larger contributions can qualify for designating seminar rooms and other areas.

Finally, why am I so concerned about Heart House becoming a reality? Why should you be? It is obvious that continuing education is a must for the busy practitioner. Self-assessment examinations and recertification examinations will become a way of life. The Board of Medical Specialists has recently indicated that voluntary periodic recertification examinations have been formally approved by 19 of 22 specialty boards. One board, the American Board of Family Practice, has made periodic recertification mandatory. Thus we cannot escape any longer demands of the public for evidence of continuing education and competence in patient care. Those of us who do not have boards should not fear if we continue to learn and "keep up." Heart House will ensure that self-assessment and examination techniques will be available for noncertified physicians so that they can assure the public that they are knowledgeable in the latest that the science of medicine can offer.

Thus, Heart House is a personal necessity for all of us who care for patients.

Henry D. McIntosh, MD, FACC
President
American College of Cardiology

1974–75 Committee Appointments

The following physicians have been named to the College Committees listed below:

ADMINISTRATIVE COMMITTEES

Awards Committee

Forrest H. Adams, Chairman, 1976
California
C. Richard Conti, 1977
Maryland
W. Proctor Harvey, 1976
District of Columbia
Thomas N. James, 1976
Alabama
Hilliard J. Katz, 1975
California
T. Joseph Reeves, 1977
Texas

Budget, Finance and Investment Committee

Warren J. Taylor, Chairman, 1975
Massachusetts
Melvin D. Cheitlin, 1976
Maryland
John J. Curry, 1975
Maryland

Constitution and Bylaws Committee

Robert W. Oblath, Chairman, 1976
California
Robert C. Tarazi, 1977
Ohio
Robert E. Whalen, 1977
North Carolina

Credentials Committee

Dean T. Mason, Chairman, 1976
California
L. Julian Haywood, 1975
California
Dan G. McNamara, 1976
Texas
Peter V. Moulder, 1975
Florida
Walt F. Weaver, 1976
Nebraska

Executive Committee

Henry D. McIntosh, Chairman, 1976
Texas
Charles Fisch, 1977
Indiana
William Likoff, 1975
Pennsylvania
Edward S. Orgain, 1975
North Carolina
H. J. C. Swan, 1975
California
Warren J. Taylor, 1975
Massachusetts

Government Relations Committee

Sylvan L. Weinberg, Chairman, 1976
Ohio
William A. Sodeman, Vice Chairman, 1975
Pennsylvania
Arthur C. Beall, Jr., 1976
Texas
David B. Carmichael, Jr., 1976
California
Samuel M. Fox, III, 1976
District of Columbia
Laurence A. Grossman, 1976
Tennessee
Herman K. Hellerstein, 1975
Ohio
George V. Irons, Jr., 1977
North Carolina
James A. Kaufmann, 1977
Georgia
John M. Packard, 1975
Alabama
Robert L. VanCitters, 1975
Washington

Long Range Planning Committee

Charles Fisch, Chairman, 1975
Indiana
Walter H. Abelmann, 1976
Massachusetts
Arthur C. Beall, Jr., 1975
Texas
Henry W. Blackburn, Jr., 1975
Minnesota
E. Grey Dimond, 1975
Missouri
Robert S. Eliot, 1975
Nebraska
Mary Allen Engle, 1976
New York
Robert J. Hall, 1977
Texas
Dean T. Mason, 1976
California
Robert W. Oblath, 1976
California
Warren J. Taylor, 1975
Massachusetts

Membership Committee

Seymoure Krause, Chairman, 1977
Pennsylvania
Paul E. Ebert, 1975
New York
Ralph Eugene Smith, 1976
Minnesota

Nominating Committee

Robert O. Brandenberg, 1975
Minnesota
Samuel M. Fox, III, 1976
District of Columbia

Oscar Magidson, 1976
California
Charles E. Rackley, 1977
Alabama
David C. Sabiston, Jr., 1977
North Carolina
Harry F. Zinsser, 1975
Pennsylvania

EDUCATIONAL COMMITTEES

ACCEL Committee

E. Grey Dimond, Chairman,
Missouri
James E. Crockett,
Missouri
James H. Getzen,
California
Murray S. Hoffman,
Colorado
Suzanne B. Knoebel,
Indiana
B. L. Martz,
Missouri
Robert W. Oblath,
California
Herbert D. Ruttenberg,
Utah
Alfred Soffer,
Illinois

Annual Scientific Session Program Committee

Robert J. Luchi, Chairman,
Texas
Paul A. Ebert,
New York
Mark L. Entman,
Texas
Louis Gillespie, Jr.,
District of Columbia
Samuel Kaplan,
Ohio
Suzanne B. Knoebel,
Indiana
Richard P. Lewis,
Ohio
Harold L. Osher,
Maine
John H. Phillips, Jr.,
Louisiana
Richard L. Popp,
California
William C. Roberts,
Maryland
Richard O. Russell, Jr.,
Alabama
Ralph Shabetai,
Kentucky
Borys Surawicz,
Kentucky

Bethesda Conferences Committee

Arthur C. Beall, Jr., Chairman, 1975
Texas
Leonard S. Dreifus, Vice Chairman, 1977
Pennsylvania
Myrvin H. Ellestad, 1975
California
Leon Resnekov, 1976
Illinois

Continuing Education Programs Committee

William Likoff, Chairman, 1975
Pennsylvania
Lawrence S. Cohen, 1975
Connecticut
Robert D. Conn, 1976
Illinois
Robert S. Eliot, 1976
Nebraska
Michael S. Gordon, 1976
Florida
George C. Griffith, 1977
California
Donald F. Leon, 1977
Pennsylvania
Jere H. Mitchell, 1977
Texas
Joseph K. Perloff, 1975
Philadelphia
Philip Samet, 1975
Florida
Leonard Scherlis, 1977
Maryland
Arthur Selzer, 1975
California
John A. Spittell, Jr., 1975
Minnesota
Borys Surawicz, 1975
Kentucky
Arnold M. Weissler, 1977
Michigan

Heart House Committee

B. L. Martz, Chairman,
Missouri
Forrest H. Adams,
California
Simon Dack,
New York
E. Grey Dimond,
Missouri
Donald A. Dupler,
Pennsylvania
Charles Fisch,
Indiana
Samuel M. Fox, III,
District of Columbia
George C. Griffith,
California
Dwight E. Harken,
Massachusetts
Suzanne B. Knoebel,
Indiana
Kenneth G. Kohlstaedt,
Indiana
William Likoff,
Pennsylvania
Henry D. McIntosh,
Texas
Dean T. Mason,
California
Robert W. Oblath,
California
William C. Roberts,
Maryland
William A. Sodeman,
Pennsylvania
H. J. C. Swan,
California
Henry A. Zimmerman,
Ohio

International Education Committee

Eliot Corday, Chairman, 1977
California
William B. Abrams, 1977
New Jersey
Nemat O. Borhani, 1975
California
Dwight E. Harken, 1976
Massachusetts
Albert Starr, 1976
Oregon

Named Scientific Lectures Committee

Dwight E. Harken, Chairman, 1977
Massachusetts
Daniel A. Brody, 1977
Tennessee
Peter L. Frommer, 1975
Maryland
Robert J. Luchi, 1975
Texas
Gardner C. McMillan, 1976
Maryland
John Ross, Jr., 1976
California

Professional Communications Committee

J. Michael Criley, Chairman, 1977
California
Gordon A. Ewy, 1977
Arizona
Dale Groom, 1976
Oklahoma
James R. Jude, 1975
Florida
John E. Merriman, 1976
Saskatchewan
Kenneth M. Rosen, 1977
Illinois

Publications Committee

John Ross, Jr., Chairman, 1977
California
W. Gerald Austen, 1976
Massachusetts
Lionel M. Bargeron, Jr., 1976
Alabama
Simon Dack (ex officio)
New York

D. Luke Glancy, 1977
Louisiana
Herbert J. Levine, 1975
Connecticut
Charles E. Rackley, 1975
Alabama

Self Evaluation Committee

Charles Fisch, Chairman, 1976
Indiana
R. Joe Noble, 1975
Indiana
Arthur Selzer, 1976
California
Borys Surawicz, 1976
Kentucky

Young Investigators' Competition Committee

William W. Parmley, Chairman, 1976
California
Willard M. Daggett, 1975
Massachusetts
William F. Friedman, 1976
California
Shah Budin H. Rahimtoola, 1975
Oregon

Ad Hoc Committee on Cardiovascular Surgery

Grady L. Hallman
Texas
W. Dudley Johnson
Wisconsin
Gerald Lemole
Pennsylvania

Ad Hoc Committee on Emergency Room and Pre-Hospital Care

Leonard A. Cobb, Jr., Chairman
Washington
Gary J. Anderson
Indiana
Roy M. Baker
Florida
Hilliard J. Katz
California
Max Harry Weil
California

Ad Hoc Committee on Geriatrics

Raymond Harris, Chairman
New York
George E. Burch
Louisiana
Dwight E. Harken
Massachusetts
Maurice Lev
Illinois
Aldo A. Luisada
Illinois

Ad Hoc Committee on Foreign Chapters

Eliot Corday, Chairman
California
Richard L. Popp
California
Charles E. Rackley
Alabama

Ad Hoc Committee on Mace

William A. Sodeman, Chairman
Pennsylvania
Clifford B. Cherry
California
George C. Griffith
California

Ad Hoc Committee on Pediatric Cardiology

Samuel Kaplan, Chairman
Ohio
Dan G. McNamara
Texas
James J. Nora
Colorado
Saul J. Robinson
California
Madison S. Spach
North Carolina

COLLEGE REPRESENTATIVES TO OTHER ORGANIZATIONS

American Association for the Advancement of Science

Edward W. Hawthorne

The American Board of Internal Medicine and Subspecialty Board in Cardiovascular Disease

Liaison

Henry D. McIntosh
Charles Fisch
H. J. C. Swan

American College of Chest Physicians

Liaison with Government Relations Committee

Sylvan L. Weinberg

American College of Surgeons

Robert J. Hall
Jack M. Matloff

American Heart Association

Liaison with Annual Scientific Program Committee

Robert J. Luchi

Joint Officers Committee

Henry D. McIntosh
Charles Fisch
H. J. C. Swan
William D. Nelligan

American Medical Association

Current Medical Terminology Project

Bernard L. Segal

Interspecialty Council

Charles Fisch, Delegate
Henry D. McIntosh, Alternate Delegate

Section on Cardiovascular Disease

George E. Burch, Chairman
David B. Carmichael, Jr.
Simon Dack
William J. Grace
Harold I. Griffeath
Robert W. Oblath
William A. Sodeman

Audio Engineering Society

Stethoscope Standards Subcommittee

Dale Groom

Inter-Society Commission on Heart Disease Resources

Samuel M. Fox, III

Inter-Society Committee on Multiphasic Health Screening

David M. Berkson
Sylvan L. Weinberg

National Society for Medical Research Council

William H. Wehrmacher

National Heart and Lung Institute

Liaison with Institute Director

Charles Fisch
Henry D. McIntosh
Sylvan L. Weinberg

VIIth WORLD CONGRESS OF CARDIOLOGY

The VIIth World Congress of Cardiology will be held in Buenos Aires, Argentine Republic, September 1 to 7, 1974. The Buenos Aires Sheraton Hotel will be the headquarters for sessions and exhibitions.

The scientific meetings will consist of Principal Sessions, Round Tables, Conferences, Free Communications, Luncheon Panels and Talks with Experts. In addition to the scientific program and scientific, commercial and industrial exhibitions, a full social program with scheduled tours and visits to museums and shows has been planned.

For further information, write the Secretary General, Dr. Bernardo Malamud, Avda. Roque S. Peña 1110, 2º piso, Buenos Aires, Argentina. Cables: CENIBAIRES.

Advance Program

Annual Meeting of the American Medical Association

Section on Cardiovascular Disease
Chicago, Illinois, June 25, 1974

A PRACTITIONER'S APPROACH TO ANGINA IN 1974

MORNING SESSION: 9:00 AM TO 12 NOON

Angina Pectoris

Introduction

William J. Grace, MD, Director of Medicine, St. Vincent's Hospital; Professor of Clinical Medicine, New York University School of Medicine, New York, New York.

Pain Patterns in Angina Pectoris. Clinical Clues to a Bedside Diagnosis.

John R. Tobin, Jr., MD, Professor and Chairman, Department of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Auscultatory and Electrocardiographic Manifestations of Coronary Artery Disease.

James V. Talano, MD, Assistant Professor of Medicine and Assistant Director, Cardiac Catheterization Laboratory. Loyola University Stritch School of Medicine, Maywood, Illinois.

Anatomic and Angiographic Features of Coronary Artery Disease.

William Towne, MD, Assistant Director Cardiac Catheterization Laboratory, Veterans Administration Hospital, Hines, Illinois. Instructor in Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Break

Localization of the Atherosclerotic Plaque in Coronary Artery Disease.

Gissur Brynjolfsson, MD, Professor and Chairman, Department of Pathology, Loyola University Stritch School of Medicine, Maywood, Illinois.

A Physiologic Approach to Angina Pectoris.

Henry S. Loeb, MD, Associate Program Director, Section of Cardiology, Veterans Administration Hospital, Hines, Illinois. Associate Professor of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Panel Discussion and Questions

Lunch

AFTERNOON SESSION: 1:00 PM TO 5:00 PM

Modern Approach to the Patient with Angina Pectoris

Management of Risk Factors and Pattern of Lipoprotein and Abnormalities in the Patient with Angina Pectoris.

David M. Berkson, MD, Associate Professor, Department of Community Health and Preventive Medicine, Northwestern University Medical School, Chicago, Illinois.

Use of Exercise Stress Testing in the Evaluation of the Patient with Chest Pain: Reliability and Safety.

John F. Moran, MD, Director of Graphic Laboratory and Assistant Professor of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Syndromes Which Mimic Angina Pectoris and Their Management.

Rimgaudas Nemickas, MD, Associate Chief Section of Cardiology and Associate Professor of MEDICINE= Loyola University Stritch School of Medicine, Maywood, Illinois.

An Approach to the Medical Management of Stable Angina Pectoris.

Leon Resnekov, MD, Joint Director, Section of Cardiology and Professor of Medicine, University of Chicago Hospitals, Chicago, Illinois.

Panel Discussion

Break

Management of the Patient with Pre-Infarction Angina; Indications and Risk of Angiography.

Patrick J. Scanlon, MD, Director, Catheterization Laboratory and Assistant Professor of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Follow-up of Patients Undergoing Coronary Artery Surgery for Angina Pectoris.

Roque Pifarre, MD, Chief, Cardiac Surgery Section and Professor of Surgery, Loyola University Stritch School of Medicine, Maywood, Illinois. Chief, Cardiopulmonary Surgical Section, Veterans Administration Hospital, Hines, Illinois.

When is Surgery Indicated in the Patient with Coronary Artery Disease?

Rolf M. Gunnar, MD, Chief, Section of Cardiology and Professor of Medicine, Loyola University Stritch School of Medicine. Program Director, Section of Cardiology, Veterans Administration Hospital, Hines, Illinois.

The Natural History of Angina Pectoris: An Overview of the Problem.

Oglesby Paul, MD, Professor of Medicine, Northwestern University Medical School, Chicago, Illinois.

Panel Discussion

For further information write American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.
ogy, 9650 Rockville Pike, Bethesda, Md. 20014.

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

MAY AND JUNE, 1974

MAY 6–9 **The Recognition and Management of Coronary Syndromes.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 9–11 **The Ventricular Ectopic Beat: Heart-throb or Harbinger of Death.** Bernard Tabatznik and J. O'Neal Humphries, FACC, directors. Cross Keys Inn, Baltimore, Md.

MAY 15–17 **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director. Georgetown University School of Medicine, Washington, D. C.

MAY 17–19 **Core Curriculum: Rational Drug Therapy in Cardiovascular Disease.** Robert J. Lee, PhD., director. The Nassau Inn, Princeton, N. J.

MAY 23–25 **Cardiologist's Appraisal of Operable Heart Disease.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. St. Francis Hotel, San Francisco, Calif.

JUNE 6–8 **Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** Arthur D. Hagan, director and Robert A. O'Rourke, FACC, co-director. Town and Country Hotel, San Diego, Calif.

INSTRUCTIONS FOR AUTHORS

The editors and publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- **Address manuscript** to Simon Dack, MD, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- **Submit two copies** of all elements of the article: text, references, legends, tables and figures.
- **Arrange the paper** in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- **Number all pages** in above sequence, beginning with title page as 1, abstract as 2, etc.
- **Type all matter:** (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on **one side** of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- **Number title page** as page 1.
- **Include first names,** degrees and, where applicable, FACC for all authors.
- **Insert at bottom:** name and address of institution from which work originated plus information about grants.
- **Add at bottom** the phrase "Address for reprints: . . ." followed by full name and address with zip code.

THE ABSTRACT

- **Limit words as follows:** 100 to 250 words for major articles; 50 to 100 words for case reports.
- **Add at end of abstract:** an alphabetical list of 2 to 6 key words and subjects for indexing.

THE TEXT

- **Number pages** in sequence after abstract.
- **Type in duplicate;** double-space.
- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.

- **Cite in numerical** order every reference, figure and table. (Order of mention in text **determines the number** given to each.)
- **Place acknowledgments** at end of text, before references.

THE REFERENCES

- **Type in duplicate;** double-space.
- **Place immediately** after text, and number pages in sequence after text page numbers.
- **Number the references** in order in which they are mentioned in text.
- **Follow the general** arrangement, abbreviations and punctuation styles shown below.

THE FIGURE LEGENDS

- **Start at top** of new page.
- **Type in duplicate;** double-space.
- **Number pages** in sequence after last page of references.
- **Identify at** the end of each legend and **in alphabetical order** all abbreviations in the figure described.

THE TABLES

- **Start each** table at top of new page.
- **Type in duplicate;** double-space.
- **Number pages in** sequence after last page of legends.
- **Give each table** a number (in roman numerals: Table I, II, etc.) and a title. Number the tables in order in which they are mentioned in the text.
- **Provide a footnote** to each table—identifying **in alphabetical order** all abbreviations used.

THE FIGURES

- **Submit 2 glossy prints** (not originals) of each photo and drawing.

Please note that art work of published articles will not be returned.

- **Use black ink** for all charts (line drawings). Make decimals, broken lines, etc. strong enough for reproduction.
- **Use arrows** to designate special features.
- **Crop photomicrographs** to show only essential field.
- **Identify figures** on back by number and author's name.
- **Number figures** in order in which they are mentioned in the text.
- **Indicate top** of each figure.
- **Submit written permission** from publisher and author to reproduce any previously published figures.
- **Limit figures** to number necessary for clarity. The publisher allows a limited sum toward reproduction.

Examples of Styles of References

For periodicals, follow INDEX MEDICUS:

31. Bellet S, Feinberg LJ, Sandberg H, et al: The effects of caffeine on free fatty acids and blood coagulation parameters of dogs. J Pharmacol Exp Ther 159: 250-254, 1968

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

(Author: all book references should have specific page numbers)

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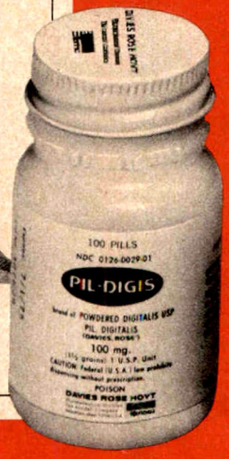

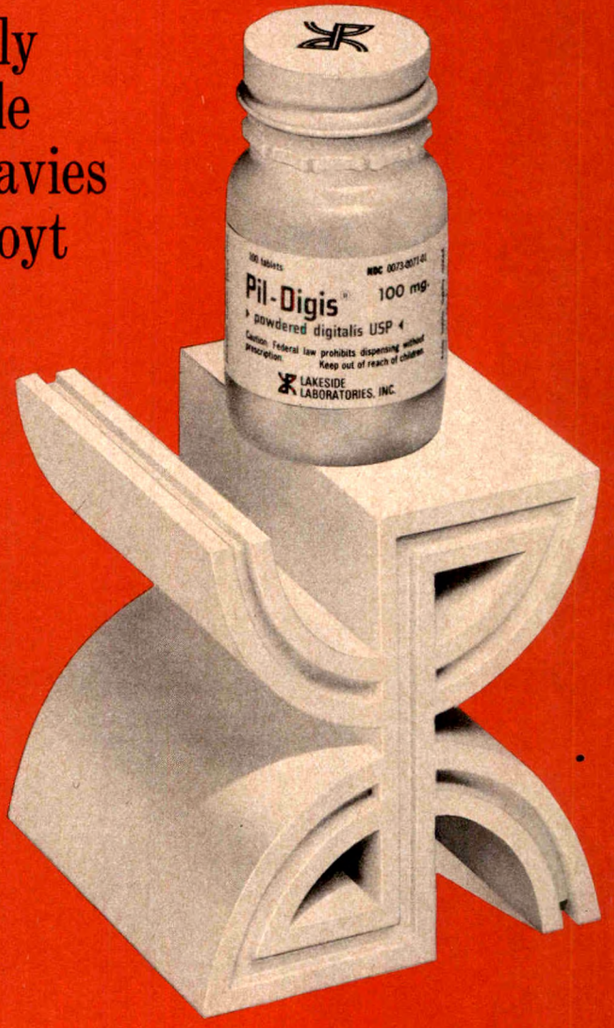

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The newest Ekoline 20A® features multi-parameter capability.

Two new modules give the Smith Kline Instruments Ekoline 20A® an unmatched multi-trace capability. The Isolated Sweep/EKG Module and the Multi-Parameter Amplifier Module enable the E20A Ultrasonoscope to produce traces for ultrasound, EKG, phono and carotid pulse or apex. Combine this with the Fiber-optic Recorder and the result is high quality, grey scale strip chart recordings of pertinent information—at a surprisingly low cost.

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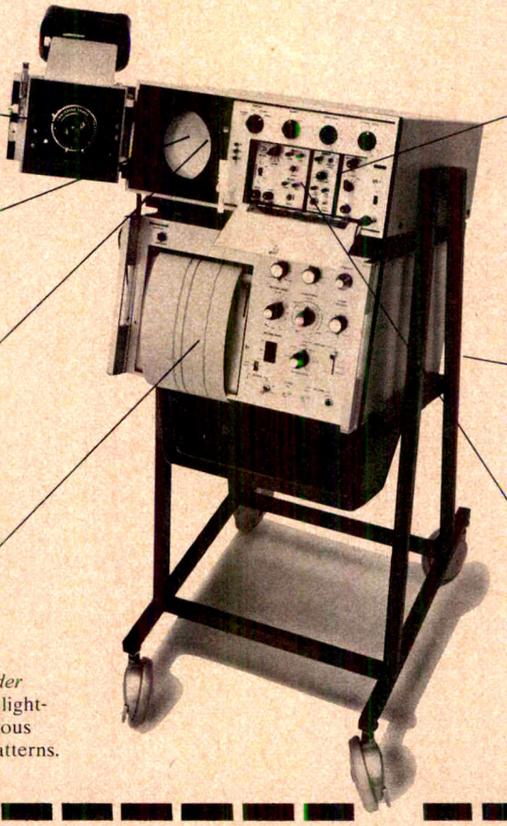
4. *New Fiber-Optic Line-Scan Recorder* utilizes fiber-optic CRT to expose light-sensitive paper, producing continuous "strip-chart" recordings of echo patterns.



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6. *New Equipment Cart* conveniently houses 'Ekoline 20A' and Recorder. Permits complete system to be readily moved to any location throughout the hospital.

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Please:

☐ Have representative call me to arrange a demonstration.

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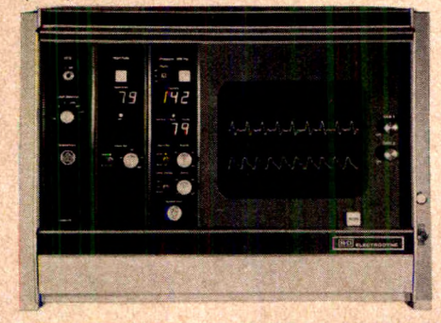

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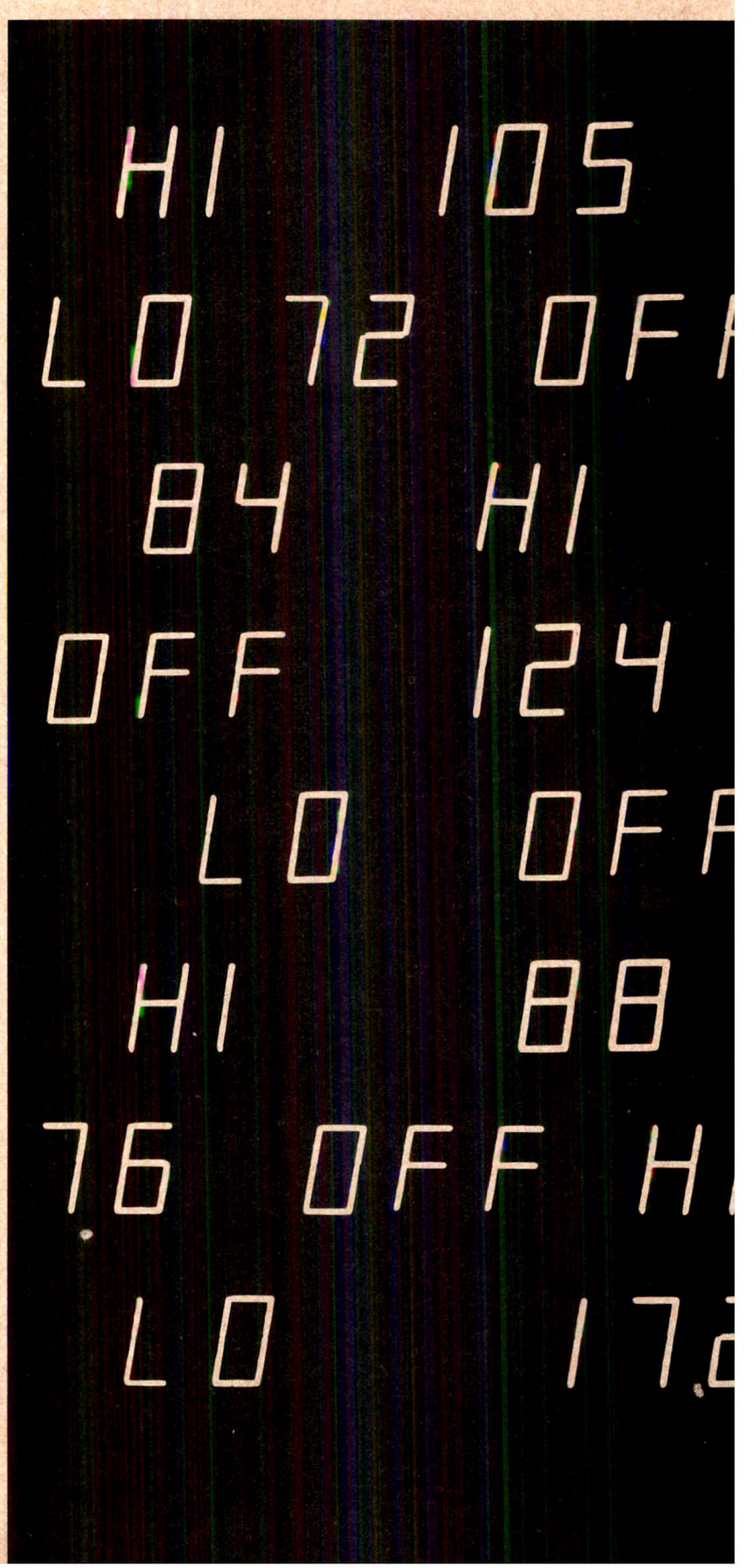

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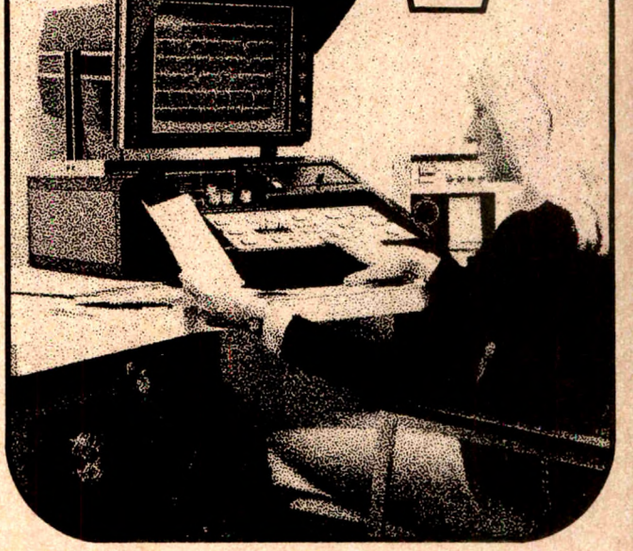

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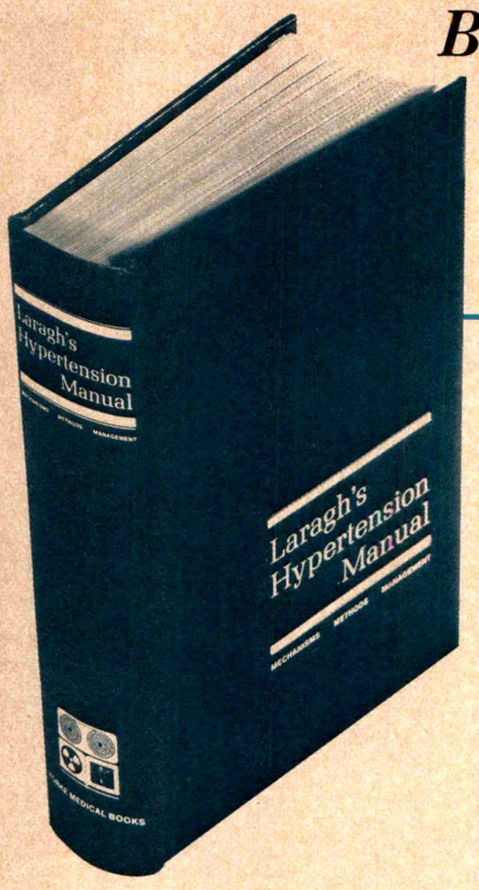

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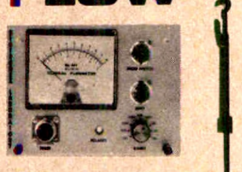

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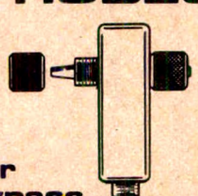

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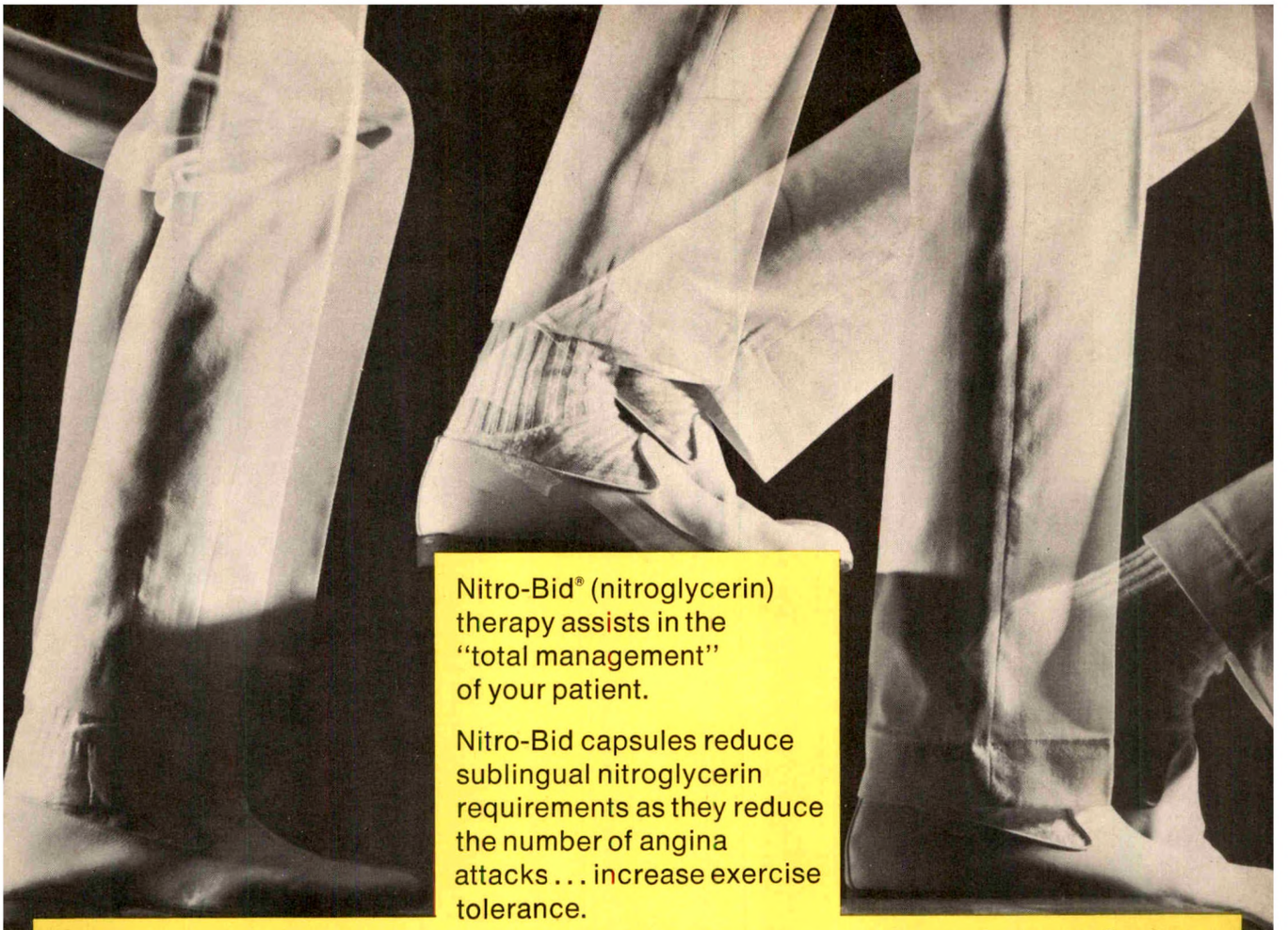

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helps reduce elevated cholesterol and/or triglycerides– not just cholesterol alone

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS
WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Hypercholesterolemia/Hypertriglyceridemia/**Atromid-S®** (clofibrate) **Ayerst®**

See last page of advertisement for prescribing information.

Atromid-S®
(clofibrate)

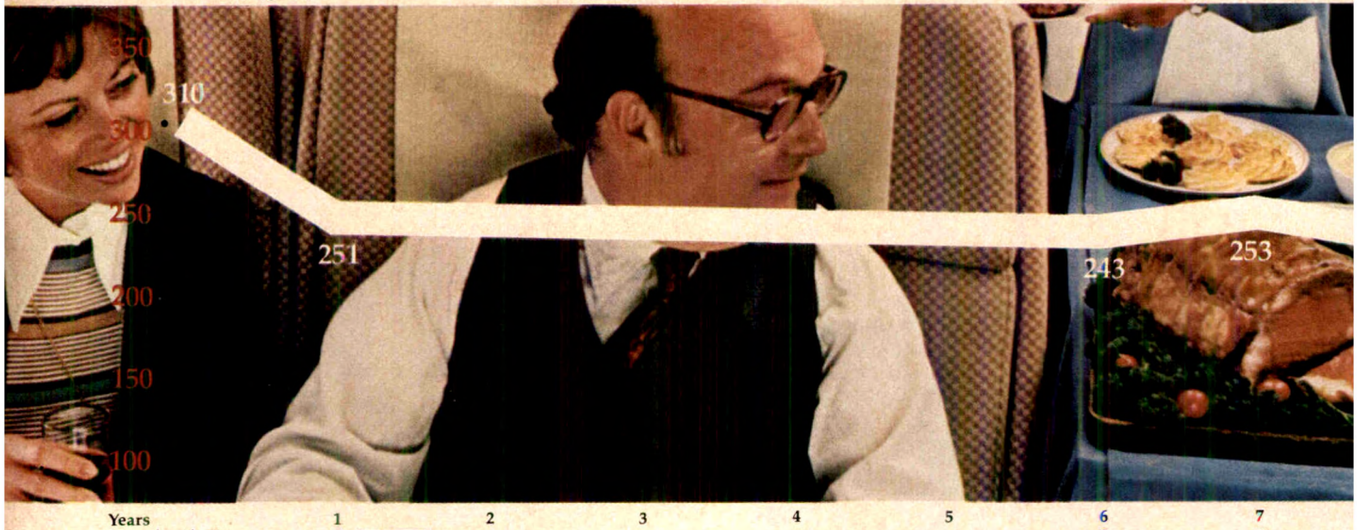
significantly lowers cholesterol and triglycerides in patien with elevated serum levels of both lipids[3]

Mean Values (mg. %) of CHOLESTEROL ▭ TRIGLYCERIDES ▭▭▭

Years	1	2	3	4	5	6	7
No. of patients	50 ▭					50	49
	42 ▭▭▭					42	42

significantly lowers cholesterol levels in patients with normal triglyceride values (<150 mg./100 r

Mean value (mg.%) of CHOLESTEROL ▭



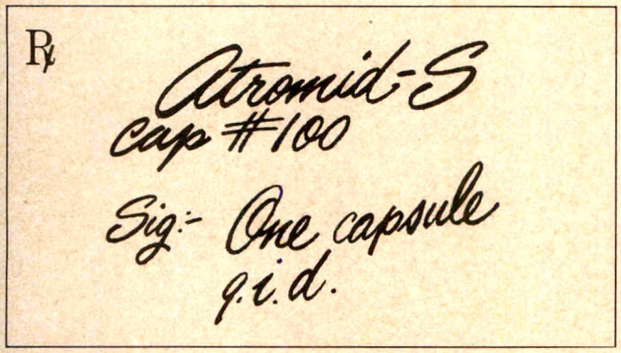
Years	1	2	3	4	5	6	7
No. of patients	8 ▭					8	7

Adapted from Berk

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholester lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coro heart disease. Several years will be required before current investigations will yield an answer to this ques

Atromid-S® (clofibrate)

helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone



BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. Hepatic biopsies are usually within normal limits. These effects are usually reversible when the drug is discontinued. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

The physician should monitor the patient with complete blood counts since peripheral anemia and, more frequently, leukopenia have been reported in patients who have been taking clofibrate. Whether these are drug-related is unknown.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus. There have been occasional cases of dry, brittle hair and of alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminases (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: increased angina, peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision.

DOSAGE AND ADMINISTRATION: Adult Dose: The recommended dosage for adults is one capsule (500 mg.) four times daily.

In Children: Insufficient studies have been done in children to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969 vol. 4, p. 314. **2.** Powell, R. C.: Resident-Intern Consultant 2:29 (June) 1973. 3. Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971.

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Let's face it. Conventional nitroglycerin is a notably unstable compound. It migrates from tablet to tablet, from tablet to cotton, from cotton to cap. Result: a wide variance in potency and therapeutic effect.

But with Nitrostat your angina patient gets a stabilized nitroglycerin. *Stabilized for uniform potency retention.* Thus, Nitrostat does the job that sublingual nitroglycerin is *supposed* to do. And does it *consistently*—providing the same pain-relieving potency, tablet after tablet. That's why more and more physicians are turning to Nitrostat.

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Sublingual Tablets
0.6 mg (1/100 gr)
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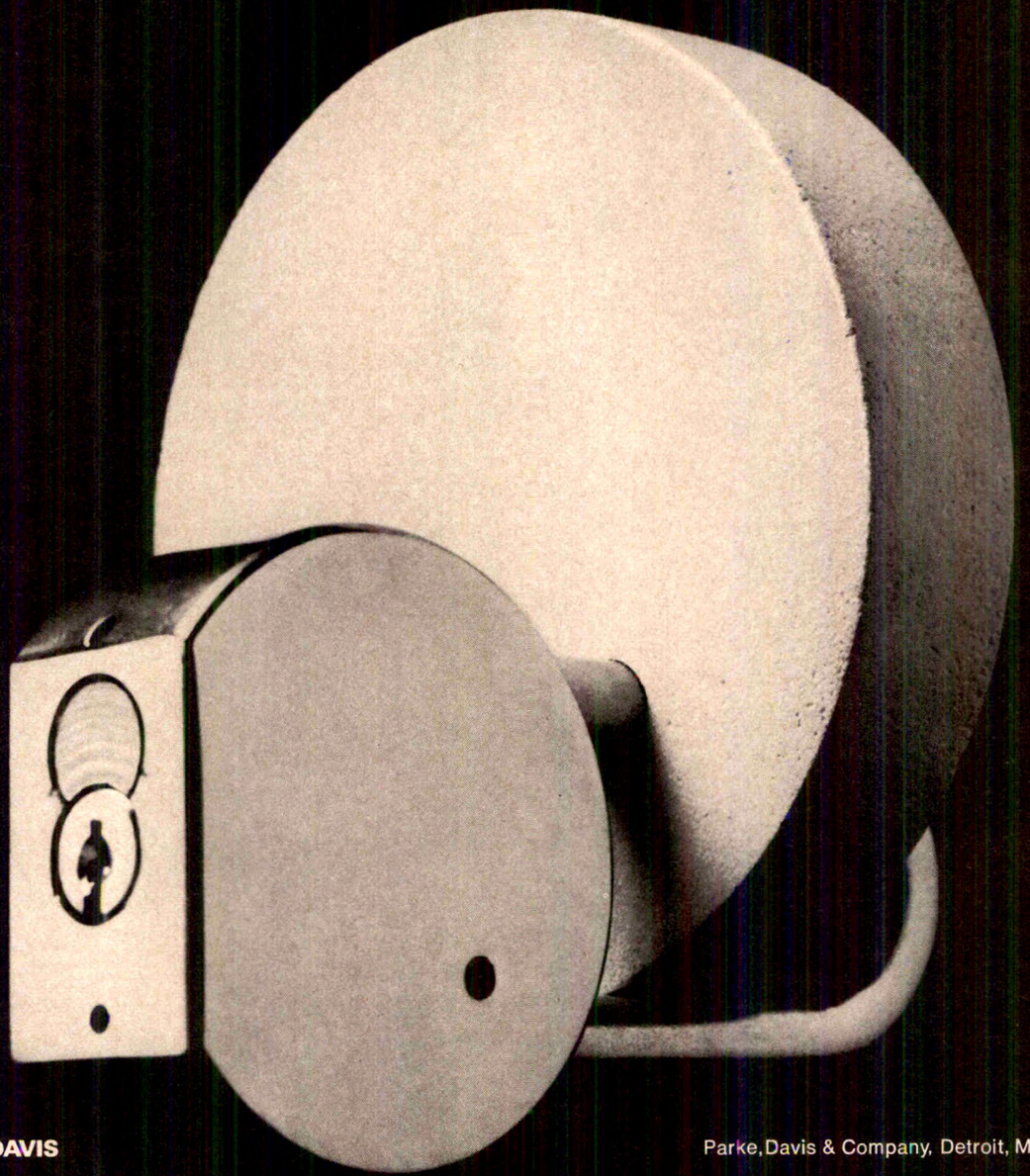
0.3 mg (1/200 gr)

Because the pain-relieving potency is locked inside–this nitroglycerin tablet will work like the next–and the next–and the next.



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THE AMERICAN JOURNAL OF CARDIOLOGY,® Official Journal of the American College of Cardiology, May 20, 1974, Vol 33, No. 6.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except May and October, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group, William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES: 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 666 Fifth Ave., New York, N.Y. 10019. Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular Issues $4.00; Symposium and Special issues $6.00 Subscription rate for individuals in field of publication: United States $20.00 a year; Canada $21.00; Foreign $28.00; Residents, Interns, and Medical Students $7.00 less than regular subscription rates. Not responsible for replacing Journal issues unless the Circulation Department is notified of nonreceipt within three months of issue date.

Second class postage paid at New York, N.Y. and additional mailing offices. Printed in U.S.A. Trademark® in U.S. Patent Office.

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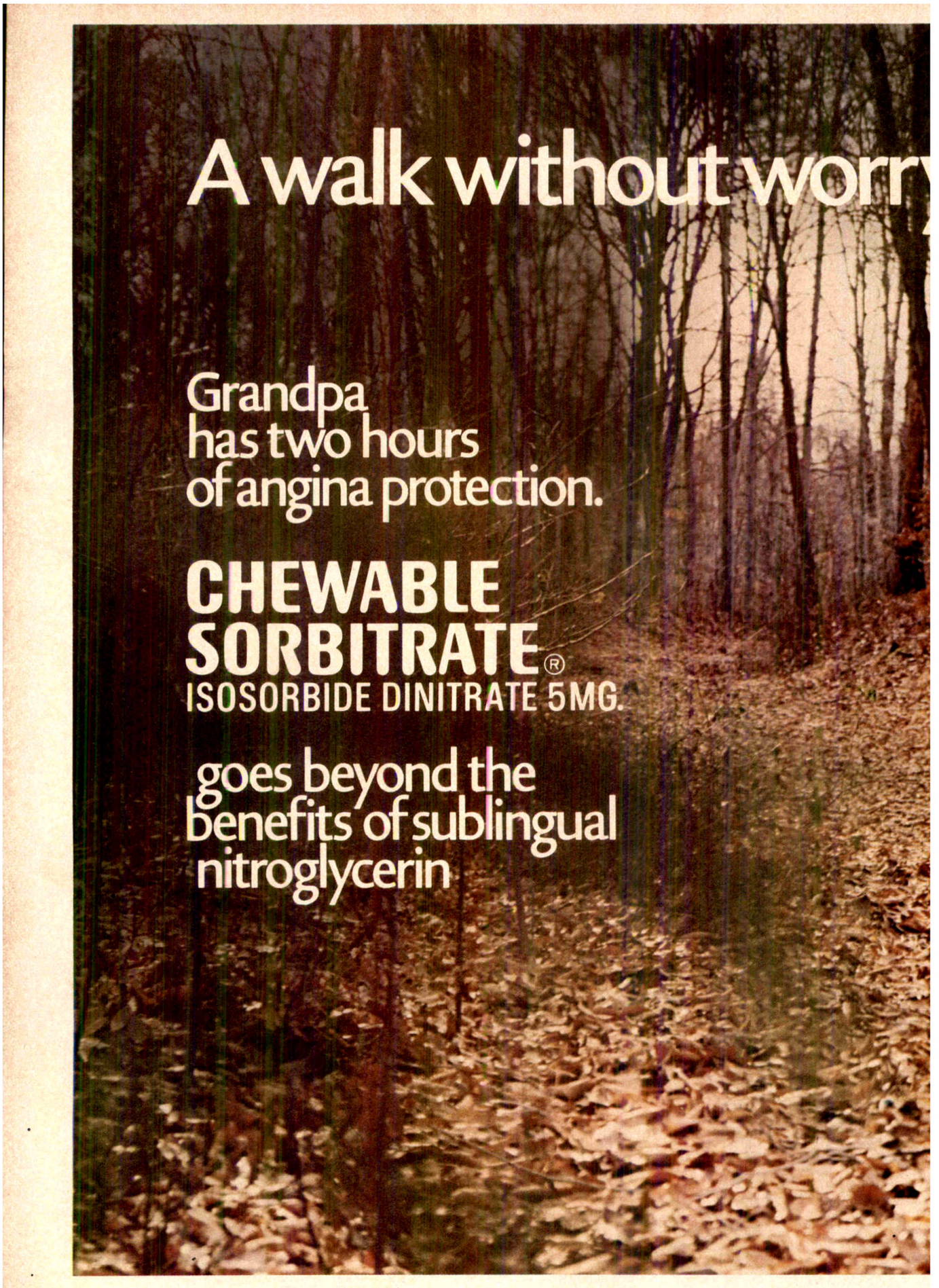
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CHEWABLE
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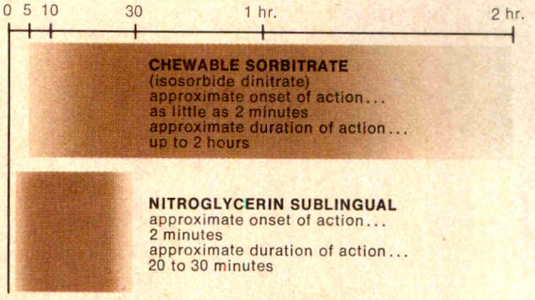
goes beyond the
benefits of sublingual
nitroglycerin

For up to two hours of protection, your angina patient needs *more* than sublingual nitroglycerin. And Chewable Sorbitrate provides more.

☐ Acts almost as fast as nitroglycerin...lasts about 4 times as long.



☐ More stable in air than sublingual nitroglycerin: it can be stored or carried with no significant loss of potency.

☐ And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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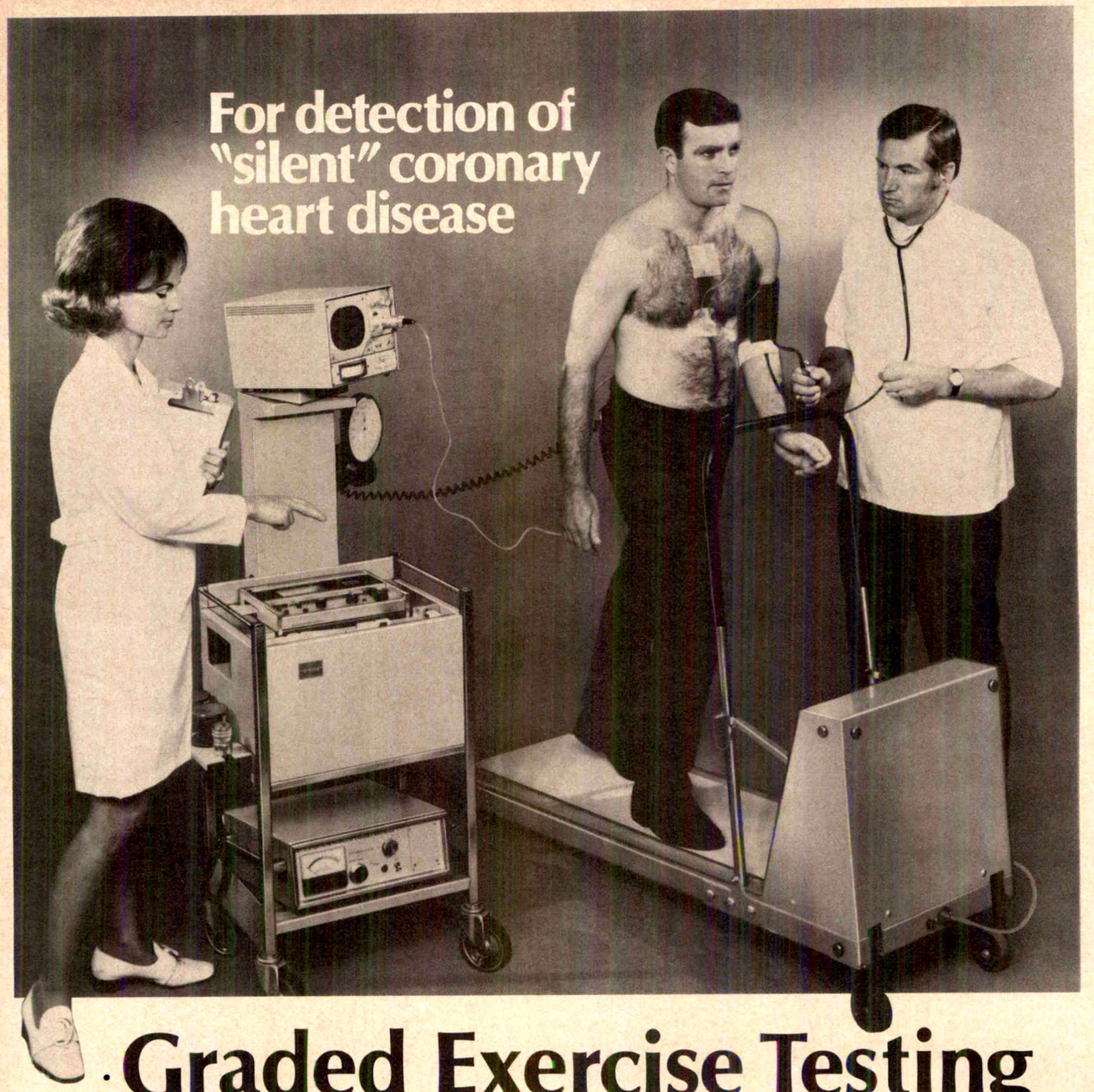

Graded Exercise Testing

The value and importance of treadmill stress-testing procedures lie in the detection of clinically unsuspected or "silent" coronary heart disease. By observing ECG responses to exercise tests, coronary disease can be detected prior to clinical manifestation in the form of angina pectoris or myocardial infarction.

Burdick's **Ex-ECG system** includes a 5″-screen cardiac monitor with integral HR-meter and 12-lead ECG preamp in combination with the **EK/5AS** automatic-start electrocardiograph and DC defibrillator—all conveniently mounted on a mobile console stand.

Versatility of the Burdick Ex-ECG system is further demonstrated by the fact the same equipment can also be utilized as an emergency cardiac station or a 1-bed ICU as needed.

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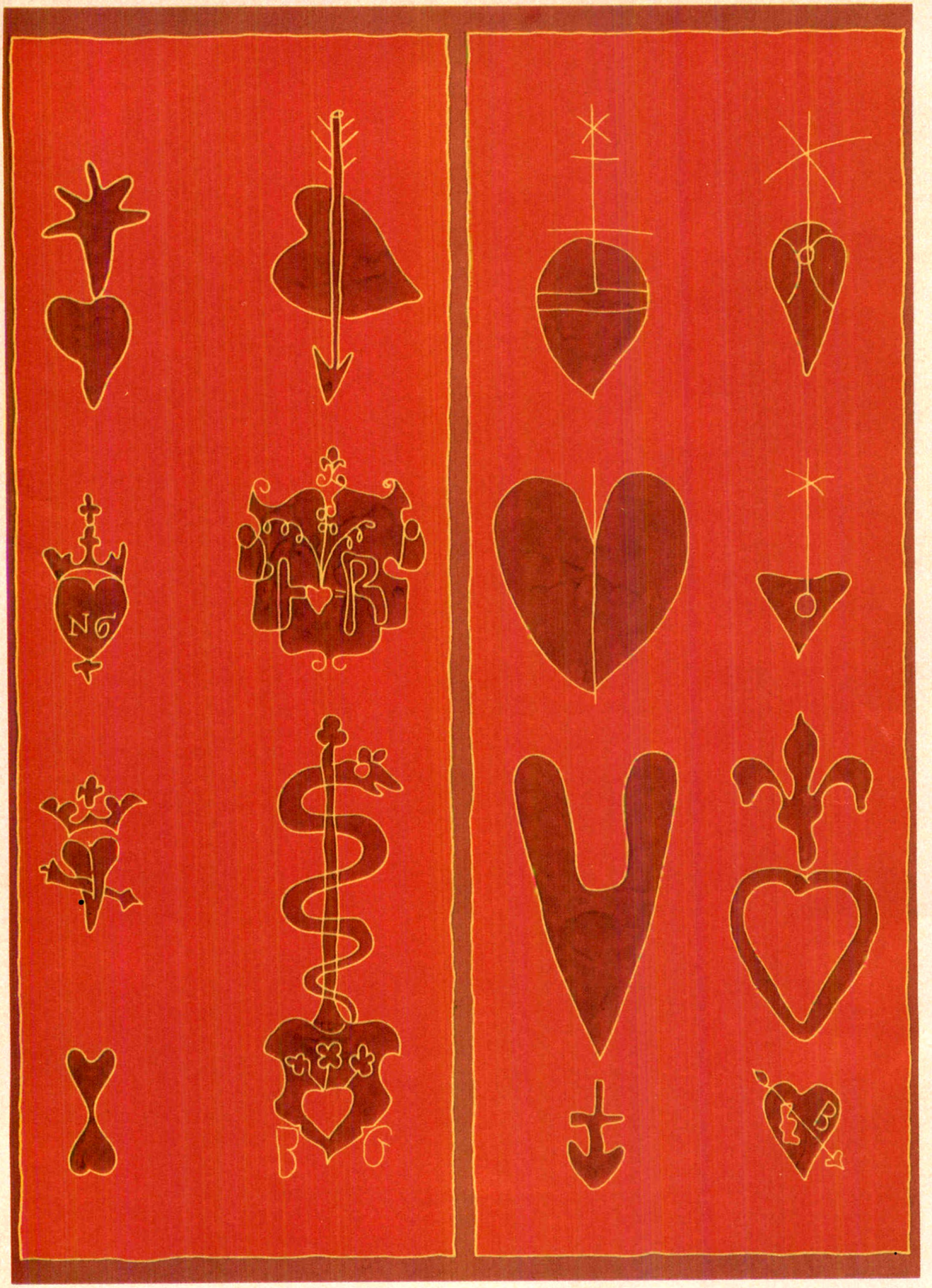

The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

Persantine — over a decade of use

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Persantine — give enough — long enough

The recommended dosage: 50 mg. t.i.d. at least one hour before meals. *Give enough, long enough* — several weeks or longer of continuous therapy may be needed to see response.

Persantine®
Tablets of 25 mg.
dipyridamole

the non-nitrate
coronary vasodilator

Heart-Shaped Watermarks
14th to 16th Century, from C. M. Briquet "Les Filigrans," Leipzig, 1923.

It was believed during the middle ages that the earth was the center of the universe and the heart was the center of man; all other organs were inferior and grouped around it. The heart was believed to be the essence of man, his most essential and noble part. In art, the heart was depicted in a variety of symbols. These heart-shaped watermarks typify the symbology of the heart.

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

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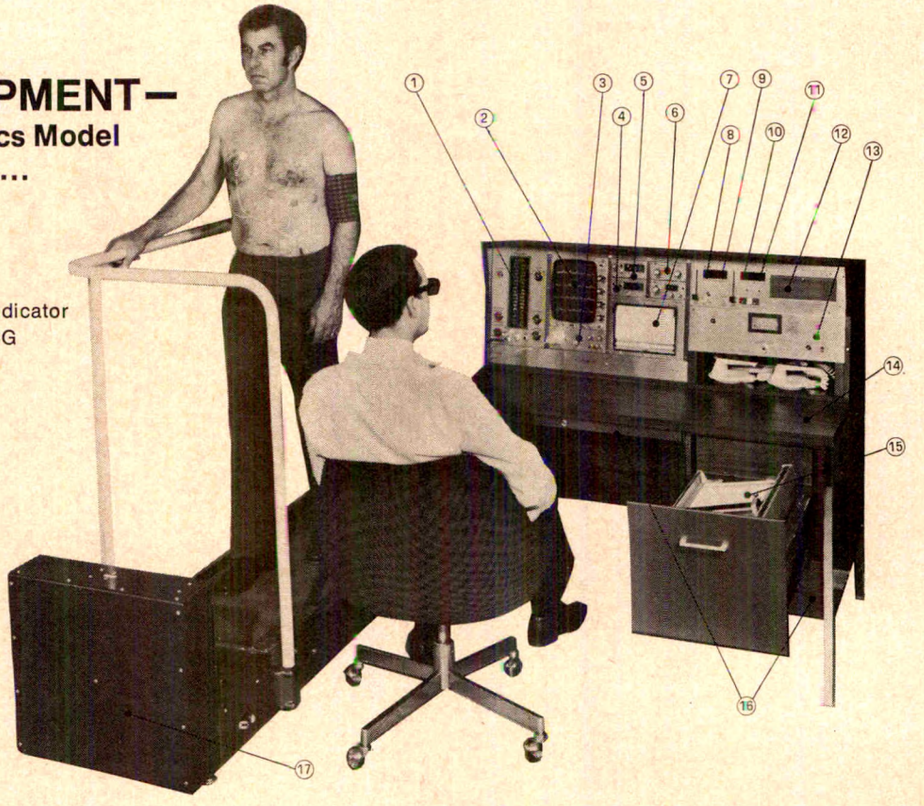

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SYMPOSIUM ON EXERCISE IN CARDIOVASCULAR HEALTH AND DISEASE

EZRA A. AMSTERDAM, JACK H. WILMORE and ANTHONY N. DeMARIA, *Guest Editors*

713 **Introduction**

715 **Methods of Exercise Testing. Step Test, Bicycle, Treadmill, Isometrics**

ROBERT A. BRUCE

This paper reviews the objectives, purposes, values and fine points of different methods currently used for exercise testing of cardiovascular function. The objectives of such studies should be to define functional aerobic capacity, the magnitude of its deviation from appropriate normal standards and the cardiovascular mechanisms of any impairment. These objectives can be met reliably with a multistage treadmill test. Clinical application of this test to identify persons at future risk for coronary artery disease is presented.

721 **Exercise Electrocardiography: Recognition of the Ischemic Response, False Positive and Negative Patterns**

ALBERT A. KATTUS

S–T segment depression in the left ventricular leads characteristic of ischemia may be obscured by conduction defects or falsely induced in patients taking digitalis or potassium-depleting drugs and in those with hypoadrenergic states, pectus excavatum or short P–R intervals. This paper discusses the significance of J point depression and the interpretation of false positive and false negative responses.

732 **Disturbances of Cardiac Rhythm and Conduction Induced by Exercise. Diagnostic, Prognostic and Therapeutic Implications**

ANTHONY N. DeMARIA, ZAKAUDDIN VERA, EZRA A. AMSTERDAM, DEAN T. MASON and RASHID A. MASSUMI

This paper review current knowledge of the electrophysiologic response of the heart to physical exertion and trends for future investigations. The presence of ventricular ectopic beats at rest does not preclude carefully performed graduated stress testing nor does their disappearance during effort exclude the presence of coronary artery disease. Ventricular premature beats that are frequent multifocal or repetitive or associated with light work loads are indicative of coronary artery disease involving two or more coronary vessels.

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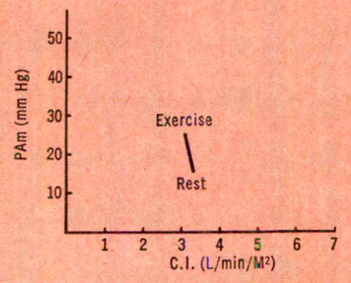
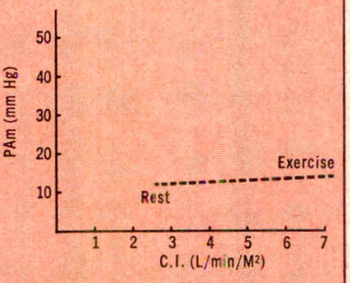
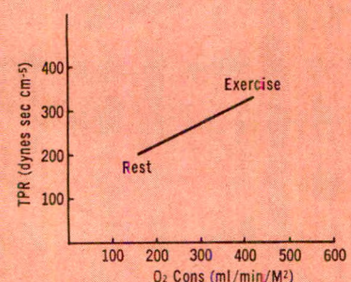
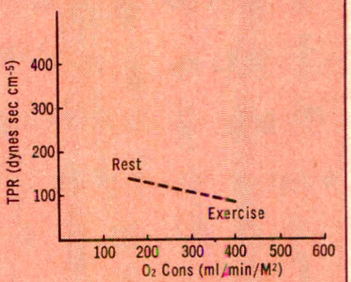
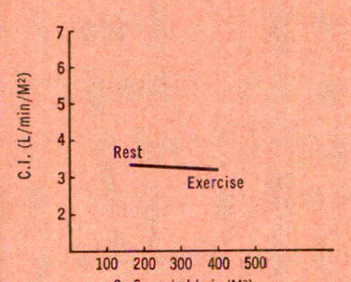
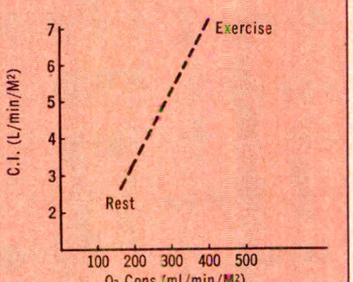
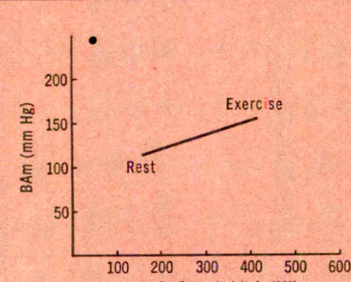
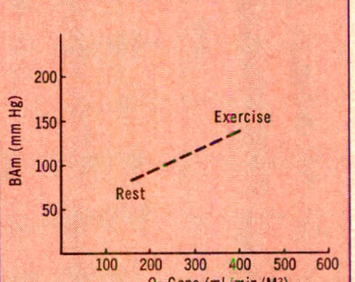
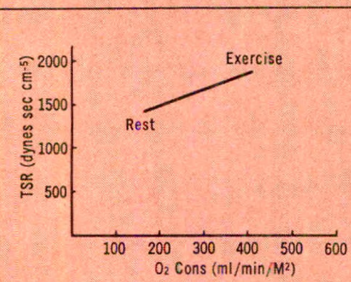
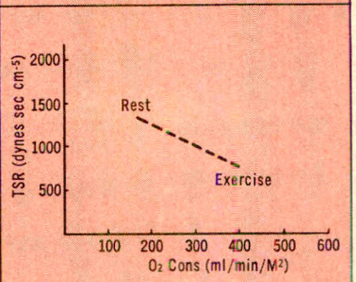
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

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Adapted from: Kasparian H, Najmi M, Likoff W: • Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.

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737 Indirect Assessment of Myocardial Oxygen Consumption in the Evaluation of Mechanisms and Therapy of Angina Pectoris

EZRA A. AMSTERDAM, JAMES L. HUGHES, III, ANTHONY N. DeMARIA, ROBERT ZELIS and DEAN T. MASON

Indirect assessment of myocardial oxygen consumption ($M\dot{V}O_2$) through derived indexes of heart rate and blood pressure, usually in the form of the product of heart rate × systolic blood pressure × systolic ejection period (triple product) or the product of the first two variables (double product), is useful for interpreting mechanisms and evaluating therapy of angina, but the technique must be applied cautiously because of the inherent limitations of these indirect indexes.

744 Experimental Observations on the Effects of Physical Training Upon Intrinsic Cardiac Physiology and Biochemistry

JAMES SCHEUER, SOMSONG PENPARGKUL and ASHOK K. BHAN

A moderate conditioning program of swimming in rats improved potential aerobic cardiac performance, producing increased capacity for coronary flow and oxygen delivery and higher levels of actomycin and myosin adenosine triphosphatase activity. Improved mechanisms of energy utilization confer partial resistance to hypoxia. Thus, hearts of conditioned rats converted chemical energy to external work more efficiently than hearts of sedentary rats.

752 Medical Screening of Patients with Coronary Artery Disease. Criteria for Entrance Into Exercise Conditioning Programs

MALCOLM M. McHENRY

This paper presents guidelines for patient safety and rejection in stress testing and training. Prospective participants in such exercise programs should be screened to assess motivation, eliminate undue risk and evaluate potential benefit. Patients with valvular heart disease, severe systemic hypertension and certain abnormal electrocardiographic patterns should be excluded.

757 Individual Exercise Prescription

JACK H. WILMORE

A successful exercise program must teach people why they should be physically active and motivate them to follow a personal activity program of endurance exercise (walk-jog-run, hiking, bicycling, swimming) at least three times weekly for 20 to 30 minutes at each session. The exercise prescription must pay attention to type of activity, frequency of participation and duration and intensity of exercise. The results from two programs using this approach show substantial improvement in the subjects' health profile.

760 Effects of Physical Training on Coronary Risk Factors

JOSEPH A. BONANNO and JAMES E. LIES

Data obtained in a 12 week, supervised physical training program for 20 exercising and 19 control subjects matched for age, occupation, coronary risk factors and physical fitness demonstrated significant improvement in physical fitness, systolic blood pressure and triglyceride levels in response to exercise, but not in cholesterol levels, smoking, obesity or psychological profile. Such a program is therapy of adjunctive value for subjects with hypertension or hypertriglyceridemia.

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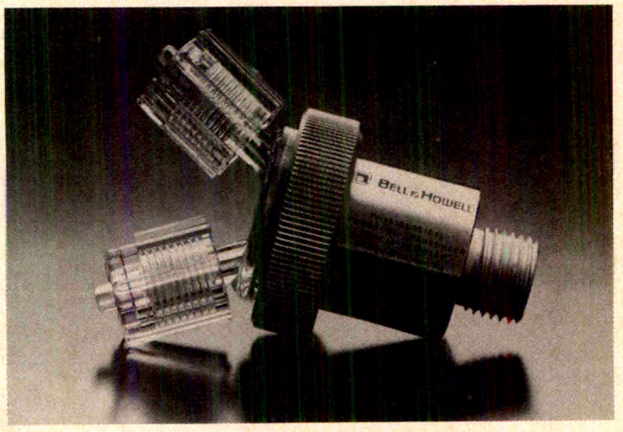

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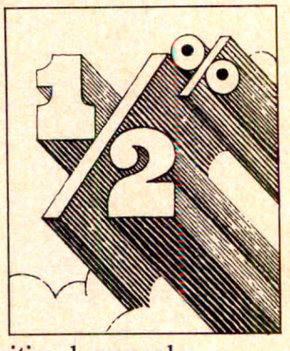

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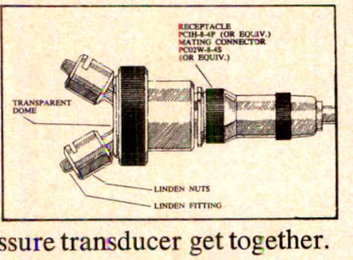

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765 **Long-Term Physiologic Adaptations to Exercise with Special Reference to Performance and Cardiorespiratory Function in Health and Disease**

WILLIAM C. ADAMS, MALCOLM M. McHENRY and EDMUND C. BERNAUER

After an excellent review of long-term physiologic adaptations of the cardiovascular system to exercise, this paper presents original data showing that after myocardial infarction most trained patients can achieve the performance levels of sedentary normal subjects except when residual disease causes myocardial dysfunction. Successful coronary artery bypass surgery rarely normalizes work performance and cardiorespiratory function although it may alleviate symptoms. Physical training in conjunction with bypass surgery improves work performance and aerobic power.

776 **Physical Activity After Myocardial Infarction**

WILLIAM L. HASKELL

Performance of physical activity by patients with uncomplicated myocardial infarction leads to earlier mobilization, reduced length of hospitalization, increased physical working capacity and more successful return to work. This article reviews the activity program in the coronary care unit, activity during the hospital stay, during convalescence and physical conditioning after recovery.

784 **Coronary Heart Disease as a Pediatric Problem. Prevention Through Behavior Modification**

JOHN L. BOYER

Alterations of behavior with emphasis on exercise of the endurance type and rational dietary habits are advocated for primary prevention of coronary heart disease in childhood. The beneficial effects of exercise may occur without alteration of coronary risk factors.

787 **Physical Fitness Programs for Adults**

KARL G. STOEDEFALKE

This paper explains the principles of exercise programs so that physicians can provide intelligent advice on this subject to their adult patients, especially those who want to do something about their "middle-age troika": weak musculature (especially of the abdomen), lack of flexibility and low endurance capability. Each adult should have a progressive exercise test before undertaking an exercise program.

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CLINICAL STUDIES

791 **Comparative Response to Isometric (Static) and Dynamic Exercise Tests in Coronary Disease**

JEAN-CLAUDE HAISSLY, ROGER MESSIN, SERGE DEGRE, POL VANDERMOTEN, BETTY DEMARET and HENRI DENOLIN

In 46 patients with arteriosclerotic heart disease the occurrence of S–T segment changes during isolated isometric exercise depended on the percent of maximal voluntary contraction applied but was less than during maximal dynamic exercise; angina seldom occurred. In 22 patients evidence of coronary insufficiency occurred more often during combined submaximal dynamic and isometric exercise than during isolated isometric exercise. The results suggest that isometric exercise tests are inadequate for diagnosing coronary insufficiency.

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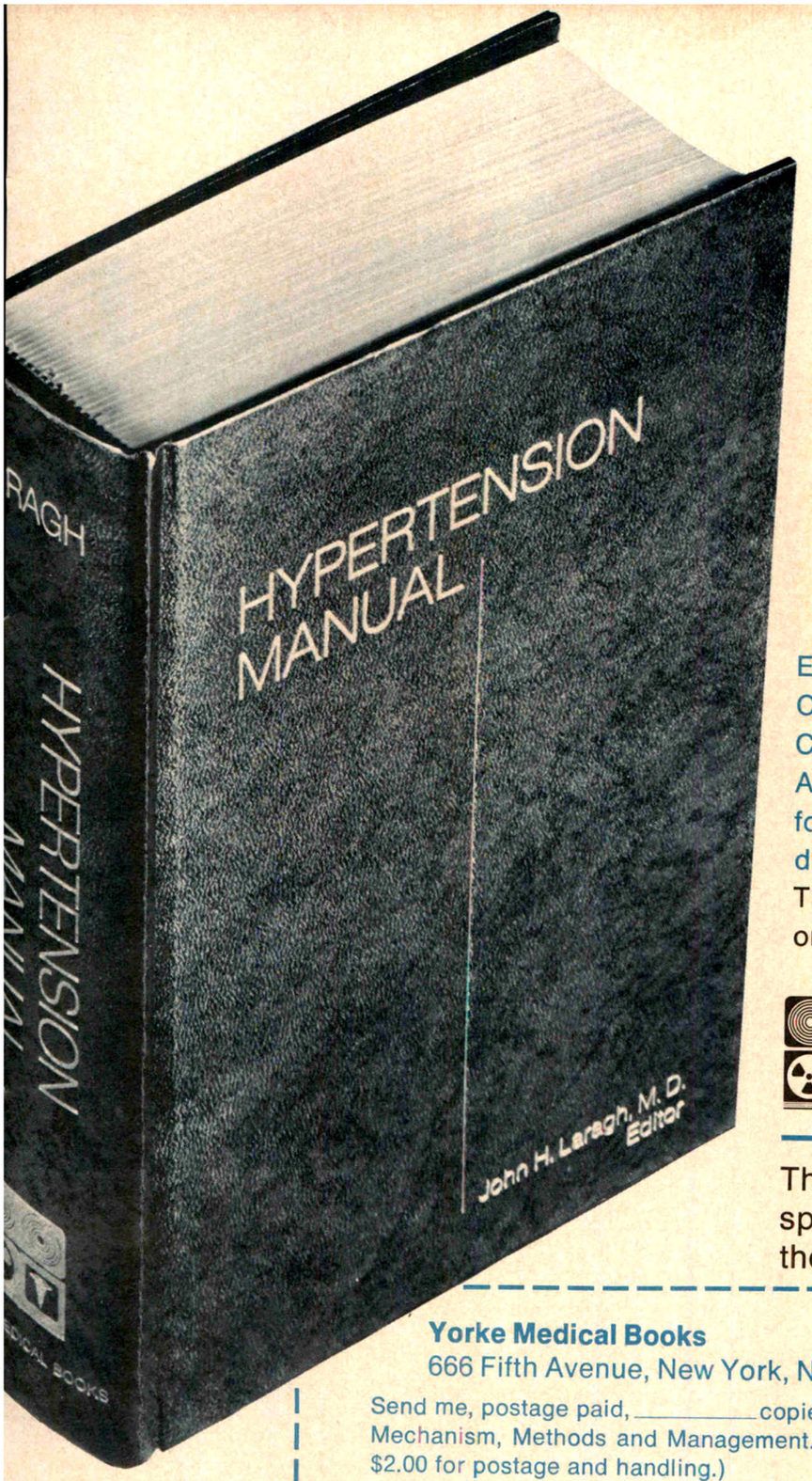

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797 Comparison of the Two-Step and Maximal Exercise Tests in Patients with Coronary Artery Disease

PAUL SCHWEITZER, V. MICHAEL JELINEK, MICHAEL V. HERMAN and RICHARD GORLIN

In 10 men with a chest pain syndrome who underwent the two-step test, maximal exercise test and coronary angiography during the same admission, neither the two-step test nor the maximal exercise test greatly helped to diagnose coronary artery disease in the patients with single vessel disease. Both exercise tests proved more sensitive in patients with multivessel disease. In certain patients the effects of augmented venous return in the supine position in increasing cardiac mechanical activity through the Starling effect may be as important a factor in eliciting ischemia as the achieved heart rate.

801 Arm-Crank Ergometry: A New Method for the Evaluation of Coronary Artery Disease

DAVID J. SHAW, MICHAEL H. CRAWFORD, JOEL S. KARLINER, GEORGE DiDONNA, RICHARD M. CARLETON, JOHN ROSS, Jr. and ROBERT A. O'ROURKE

Using a modified bicycle ergometer as an arm-crank device, these investigators conclude that arm-crank exercise is comparable to treadmill exercise and a reliable alternative method for evaluating suspected coronary artery disease in patients unable to perform leg exercise. This conclusion is based on effects on heart rate, blood pressure and S–T segment in 46 patients.

806 Effects of Perhexiline on Symptomatic and Hemodynamic Responses to Exercise in Patients with Angina Pectoris

CARL J. PEPINE, STEVEN J. SCHANG and CARL R. BEMILLER

Perhexiline given orally to 16 patients with coronary artery disease and angina pectoris favorably influenced their clinical and hemodynamic responses to exercise. This drug prevented effort-induced angina, reduced exercise tachycardia, prolonged diastolic pressure-time interval and reduced ischemia-related left ventricular dysfunction. This beneficial effect, lasting 4 hours, is attributed to enhanced myocardial oxygen delivery.

813 Myocardial Infarction After Exercise-Induced Electrocardiographic Changes in a Patient with Variant Angina Pectoris

R. LELDON SWEET and L. THOMAS SHEFFIELD

Ten minutes after a multiple stop stress test during which he achieved a maximal heart rate of 120 beats/min without symptoms this 61 year old postmaster with variant angina pectoris had an acute anterolateral wall myocardial infarction. The resting ST–T abnormality became normal during exercise. Since patients with variant angina pectoris may be particularly high risk subjects for maximal or submaximal stress testing. The use of continuous Holter monitoring may prove more physiologic and less hazardous to demonstrate the typical S–T changes during chest pain episodes.

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The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 6

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Symposium on Exercise in Cardiovascular Health and Disease

EZRA A. AMSTERDAM, MD, FACC, JACK H. WILMORE, PhD and ANTHONY N. DeMARIA, MD, *Guest Editors*

Introduction

Scientific interest in exercise as a means of disrupting man's biological homeostasis has existed for many centuries. It was not until relatively recently, however, that concerted efforts were made to gain insight into man's functional adaptability to the stress of exercise. With the establishment of the Harvard Fatigue Laboratory in 1927, a group of dedicated scientists began the systematic exploration of this major area of physiologic interest.[1] Although the Harvard Fatigue Laboratory was short-lived, continuing only until 1947, its pioneering efforts into the physiology of exercise provided the foundation for much of our present knowledge and investigation of this subject. The current application of exercise to the treatment of cardiovascular disease is but one extension of this early work. Since the introduction more than 4 decades ago[2] of systematic analysis of the circulatory response to exercise as a means of investigating cardiovasuclar status, followed by its application to the detection of latent myocardial ischemia,[3] exercise has played an increasingly important role in the diagnosis and functional evaluation of cardiac disease and, more recently, in its treatment and prevention.[4]

In recognition of the widespread interest in, and expanding application of, exercise in cardiovascular health and disease, an integrated, multidisciplinary examination of current concepts in this broad field was undertaken in the form of a conference presented by the American College of Cardiology and the University of California, Davis, School of Medicine in December 1972. This conference, "Exercise and the Heart," brought together clinicians, exercise physiologists, physical educators, epidemiologists and laboratory scientists to facilitate better understanding of exercise and its role in cardiovascular health and disease and thereby promote its more rational application in the normal population as well as in patients with cardiovascular disorders.

The proceedings at Davis have been formalized in this Symposium. The presentations divide naturally into three groups. The first four papers deal with the use and interpretation of exercise stress testing in the evaluation of cardiac disease. The second section is concerned with the effects of exercise training at experimental and clinical levels. The alterations in cardiac physiology and metabolism associated with training are explored, and the effects of conditioning on clinical cardiac disease are examined. The third group of papers is concerned with the design of effective training programs conducive to participation and adherence by appropriate subjects.

In the first paper, Bruce describes exercise testing in terms of indications, methods and respective physiologic types. His discussion focuses on assessment and clinical implications of functional aerobic impairment and electrocardiographic S–T segment changes. In the next study, Kattus addresses himself to the frequent and important clinical problem posed by interpretation of S–T segment abnormalities in evaluating the presence of myocardial ischemia. DeMaria et al. then discuss arrhythmias and conduction defects occurring during exercise stress testing and review current knowledge regarding the diagnostic, prognostic and therapeutic implications of these electrophysiologic events. The authors note that exercise may be associated with both provocation and, by overdrive suppression, abolition of ventricular arrhythmias present at rest or associated with low levels of exercise. They emphasize that the response of ventricular ectopic beats to exertion does not reliably discriminate between normal persons and patients with cardiac disease. Amsterdam et al. consider the use of exercise testing to determine the severity of

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angina. They emphasize the distinction between external work, performed by the skeletal muscles, and internal work or cardiac performance. The latter is critical to assessment of angina and can be conveniently evaluated by use of indirect hemodynamic indexes of myocardial oxygen consumption such as heart rate-blood pressure product. Within the limits of this method, which are stressed, meaningful evaluation of the mechanisms and therapy of angina can be achieved.

Scheuer et al., initiating the papers on the effects of training, provide experimental evidence of enhanced functional performance and a protective effect against hypoxic stress in association with favorable alterations in myocardial contractile proteins in hearts from trained animals as opposed to controls. The succeeding studies in this group deal with clinical application of the potential benefits of exercise training. McHenry indicates that selection of subjects for training programs entails systematic evaluation to eliminate patients at excessive risk, assess motivation and determine the individual's potential for benefit from training. Wilmore, in his discussion of the exercise prescription, directs attention to the individualization of the exercise regimen consistent with the derivation of maximal benefits. He notes that endurance activity for at least 20 to 30 minutes 3 times weekly at a target heart rate 75 percent of that associated with maximal oxygen consumption renders a significant training effect on cardiovascular functional parameters. Bonanno and Lies then evaluate the effect of such an exercise program upon coronary risk factors in clinically normal men. They demonstrate significant decreases in systolic blood pressure of hypertensive subjects and in serum triglycerides of all participants in the training program. Adams and co-workers describe their experience with exercise training in normal middle-aged men and patients who have had a myocardial infarction or aortocoronary bypass surgery. They present data to illustrate the values and limitations of a training program for these patients. Haskell considers the broad topic of physical activity at all stages in the patient who has had a myocardial infarction. He emphasizes that a training program should begin with early ambulation during the hospital phase of the illness. Such gradually progressive activity minimizes the adverse cardiovascular and psychological effects of prolonged bed rest. Regular subsequent activity based upon a carefully determined exercise prescription is associated with increased maximal oxygen consumption and work capacity.

Boyer, discussing implementation of effective training programs, the subject of the third section, emphasizes that prevention of coronary heart disease should begin in childhood. Thus, not only should early elimination of risk factors be rigorously pursued, but also adherence to patterns of exercise of the endurance type should be established in the formative years. Stoedefalke concludes the Symposium with a balanced exposition of the requisite features of a successful adult physical fitness program in which he stresses the importance of an imaginatively and individually tailored training regimen, designed and supervised by an individual well versed in the theory and practice of exercise testing.

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Methods of Exercise Testing

Step Test, Bicycle, Treadmill, Isometrics

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Methods of exercise testing are considered in relation to physiologic types, clinical applications and objectives, physiologic differences in end points and inferences, and comparison of oxygen requirements and circulatory responses. Hazards and safety precautions are cited.

The multistage treadmill test of submaximal and maximal exercise is described in terms of oxygen requirements, measurement of maximal oxygen uptake, approach to maximal uptake, determination of functional aerobic impairment and assessment of circulatory and electrocardiographic responses. Initial findings are presented of a new, prospective community study ("Seattle Heart Watch") designed to test the hypothesis that specific persons at risk for future angina pectoris, myocardial infarction or sudden death can be identified by this method.

Appraisal of exercise testing methods properly requires consideration of physiologic types of exercise, clinical applications and objectives, physiologic differences between major classes of dynamic tests, comparison of oxygen requirements and circulatory responses, recommended objectives and rationale, experience with general application and clinical evaluation of therapeutic intervention.

Physiologic Types of Muscular Exercise and Circulatory Implications

Basically, there are three types of skeletal-muscle contractions. The first type is dynamic with rhythmical contractions of extensor and flexor muscle groups. Examples of dynamic exercise include walking, stepping, pedaling, jogging and running. The alternating contractions of these muscle groups facilitate arterial inflow to the working muscles and venous return to the right heart chambers. The second type is isometric, or sustained muscle contraction. Examples of isometric exercise include handgrip, isometric weight-lifting and water-skiing. These sustained contractions limit arterial inflow by compressing small arteries and do not facilitate venous return. The third type represents the combination of the first two. Examples of this type of exercise include carrying a heavy load while walking or executing vigorous handgrips while pedaling a bicycle.

Dynamic vs. isometric exercise: Of the two major physiologic types of exercise stress, dynamic exercise is clearly preferred because the circulatory responses are directly proportional to relative aerobic requirements. In a comparative study of the two types of exercise in the same four normal subjects, blood pressure responses were exaggerated with isometric exertion (Fig. 1) and heart rate responses were greater with dynamic exercise (Fig. 2).[1] Even when each type of exertion was repeated after inadequate time for recovery, there was no significant change in these patterns. Accordingly, isometric exertion, especially if performed at a level more than 25 percent of maximal voluntary contraction, can be hazardous because the acute increases

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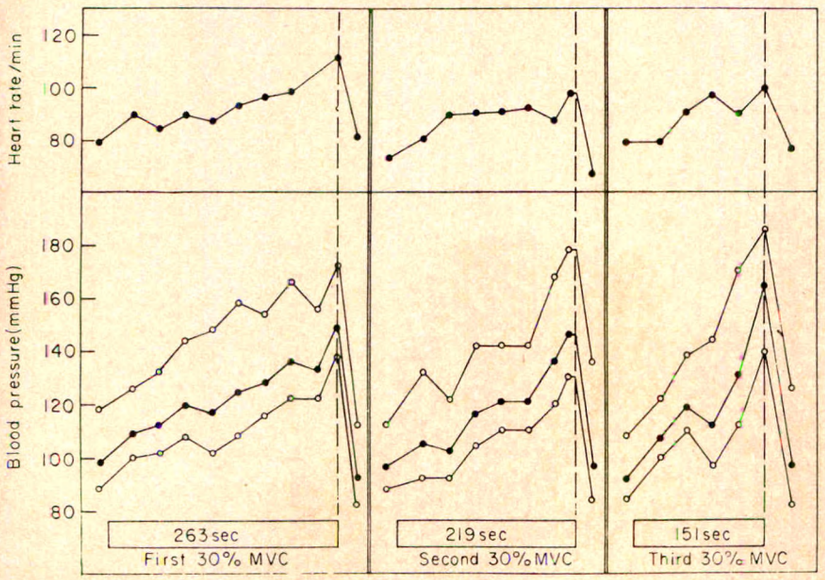

FIGURE 1. Heart rate and blood pressure responses to isometric handgrip exercise at 30 percent of maximal voluntary contraction (MVC) in four normal subjects. Note reproducibility of responses when repeated after 10 minutes **(center panel)** and after only 3 minutes **(right panel)** of recovery. (Reprinted by permission from Bruce et al.[1])

in blood pressure are greatly in excess of aerobic requirements[2] (Table I). Anecdotal data indicate hazards of acute pulmonary edema, arrhythmias, myocardial infarction and even sudden death (two instances during water-skiing) in patients with heart disease. Whatever type of stress test is used, it is important not to limit observations to electrocardiographic changes of possible myocardial ischemia of diagnostic significance, but also to note changes in rhythm, heart rate and blood pressure as indicators of circulatory impairment.

Physiologic Differences Between Major Types of Conventional Tests of Dynamic Exercise

Conventional tests of dynamic exercise can be subdivided into two major categories with important pathophysiologic differences.

Submaximal tests: These may be single stage or multistage, with continuous or discontinuous work loads and *predetermined, arbitrary* end points. These end points may be the number of trips on

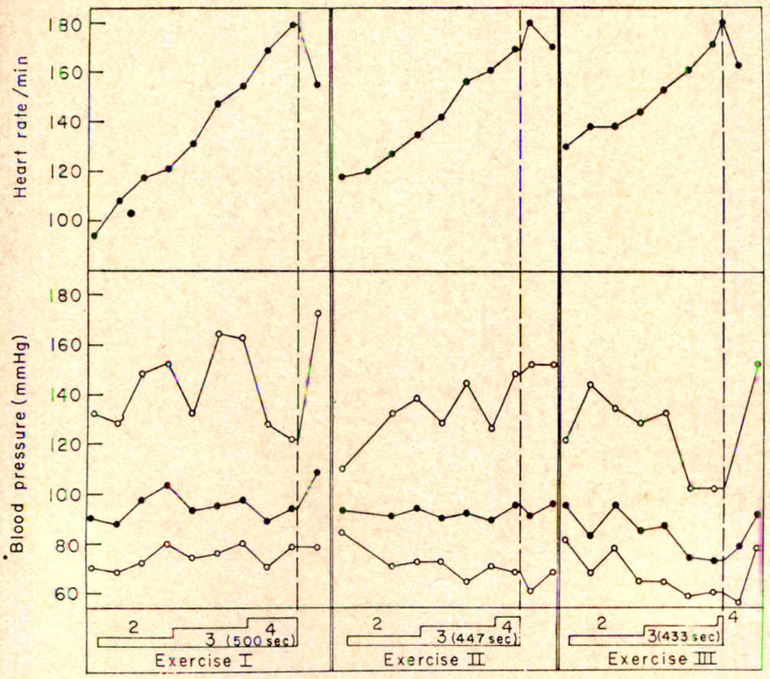

FIGURE 2. Heart rate and blood pressure responses to multistage treadmill test of dynamic exercise to maximal limits in the same four normal subjects. Again note reproducibility on repetition after only 10 minutes **(center panel)** and only 3 minutes **(right panel)** of recovery. (Reprinted by permission from Bruce et al.[1])

TABLE I

Circulatory Responses to Voluntary Handgrip, 30 Percent of Maximal, Held to Limit of Fatigue

	At Rest	Peak Response		% Change
Cutaneous circulation	Normal	Intensely hyperemic		...
Blood pressure (mm Hg)	112/82	206/142	(+94/+60)	83/73
Heart rate (beats/min)	77	92	(+15)	19

standardized steps (even when adjusted for sex, age and weight), work load, oxygen requirement or, more commonly, a target heart rate based upon a percentage of estimated maximal heart rate. The latter is obtained from age and activity status then compared with average values of "normal" persons. All these criteria fail to consider that maximal heart rate is distinctly lower in patients with heart disease, especially those with myocardial ischemia, and that the range of normal responses clearly documented by the 95 percent confidence intervals is fairly broad. Furthermore, when one of these arbitrary end points is attained, it is necessary to rely upon the subjective assessment of the patient to determine whether that arbitrary level of activity represents a low, intermediate or high fraction of his capacity. Accordingly, exercise capacity is poorly defined and, consequently, reserve function is uncertain. The majority of submaximal test procedures take into consideration that their arbitrary limits exceed the capabilities of the more impaired patient and include a variety of other indications for stopping stress, some of which may be ambiguous.

Maximal tests: Individualized, self-determined symptomatic end points of *maximal possible performances* permit each subject to attain his physiologic limit while the various symptoms, signs and circulatory, electrocardiographic and metabolic responses are observed and recorded. With a multistage treadmill protocol, this procedure has been feasible in more than 97 percent of more than 15,000 tests in our experience. These end points are more reproducible than the responses at any submaximal work load. Furthermore, with this protocol, maximal oxygen uptake and its relation to expected normal values (adjusted for sex, age and activity status) can be readily defined from elapsed time in minutes and a nomogram.

Comparison of Oxygen Requirements and Circulatory Responses

Oxygen requirements of five different submaximal exercise tests, defined by measurements in the same normal subjects, are shown in Figure 3. The greatest energy expenditure in these five tests occurred with the double Master two-step test, which required 23

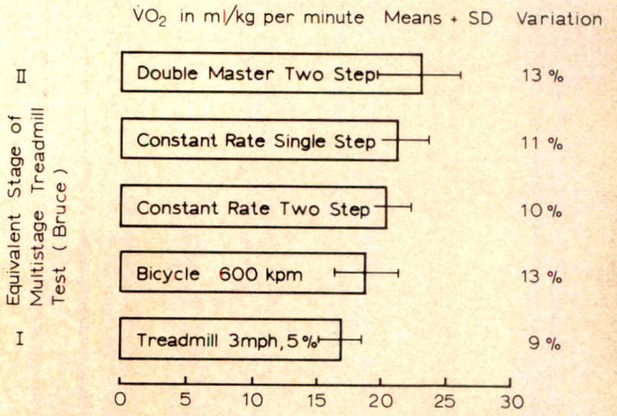

FIGURE 3. Aerobic costs of five commonly used submaximal tests. (Adapted by permission from Blackburn et al.[3]) $\dot{V}O_2max$ = maximal oxygen uptake.

ml/kg body weight per min.[3] Results of this test also exhibited the greatest variability in the relation of standard deviation to the means. The least variable, and therefore most reproducible, results were found at a low level of energy expenditure on the treadmill.

Peak oxygen uptake: Maximal tests should define the peak oxygen uptake, but when the same men are tested by different methods to a level of maximal exertion, values for oxygen uptake differ (Fig. 4). The lowest value was obtained with the bicycle ergometer, and the highest with a multistage treadmill.[5] Other studies of patients with coronary artery disease[6] indicate that ventilation as well as heart rate, arterial pressure, pressure-rate product and systemic resistance are greater in the same patients during bicycle exercise than during treadmill testing.[6] These differences are attributed to more vigorous muscle contractions with the ergometer, particularly in persons not conditioned to bicycling.

Maximal oxygen uptake ($\dot{V}O_2max$): When a multistage treadmill test of maximal exercise is used, and the subject continues exertion until a self-determined end point of fatigue or other limiting symptoms, it is remarkable that the approach to maximum

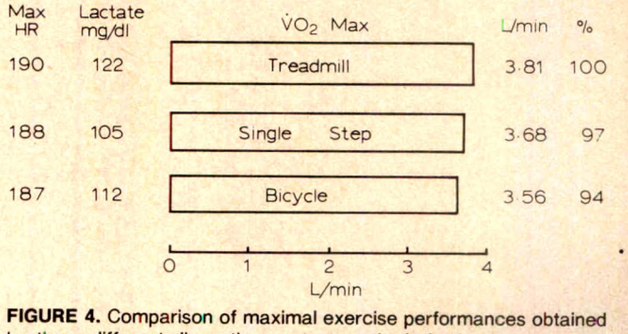

FIGURE 4. Comparison of maximal exercise performances obtained by three different discontinuous test methods in the same normal men aged 20 to 40 (mean 26.4) years. (Adapted by permission from Shephard et al.[4]) HR = heart rate; Max = maximal.

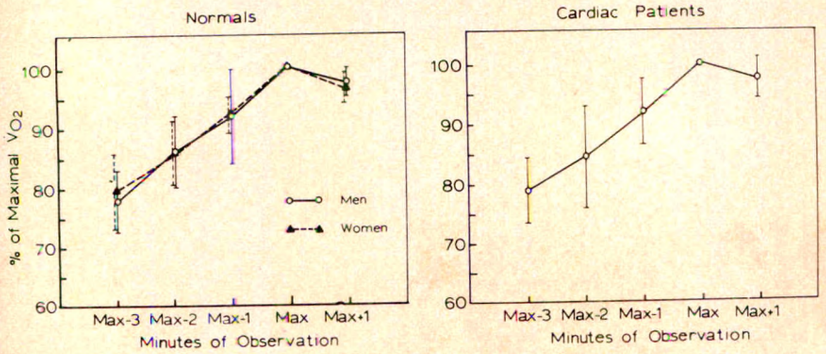

FIGURE 5. Approach to maximal oxygen uptake in normal subjects and patients with heart disease during multistage treadmill test. (Reprinted by permission from Bruce et al.[8])

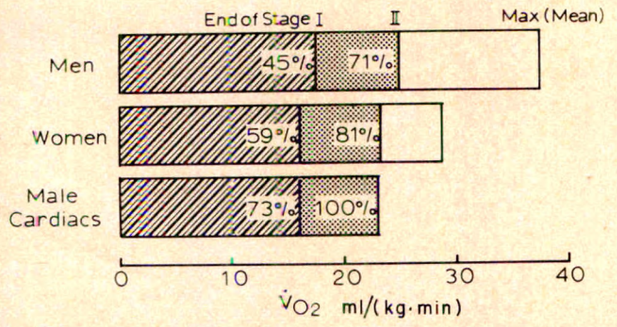

FIGURE 6. Relative aerobic requirements of submaximal exercise using multistage treadmill protocol, scaled to absolute values of maximal oxygen uptake. (Reprinted by permission from Bruce.[7])

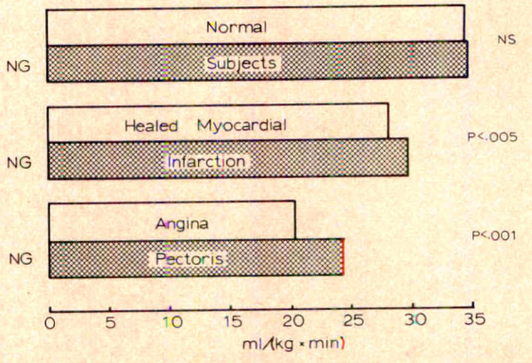

FIGURE 7. Comparison of effects of nitroglycerin on maximal oxygen uptake of patients with coronary artery disease and normal subjects. (Reprinted by permission of the American Heart Association, Inc. from Detry and Bruce.[9])

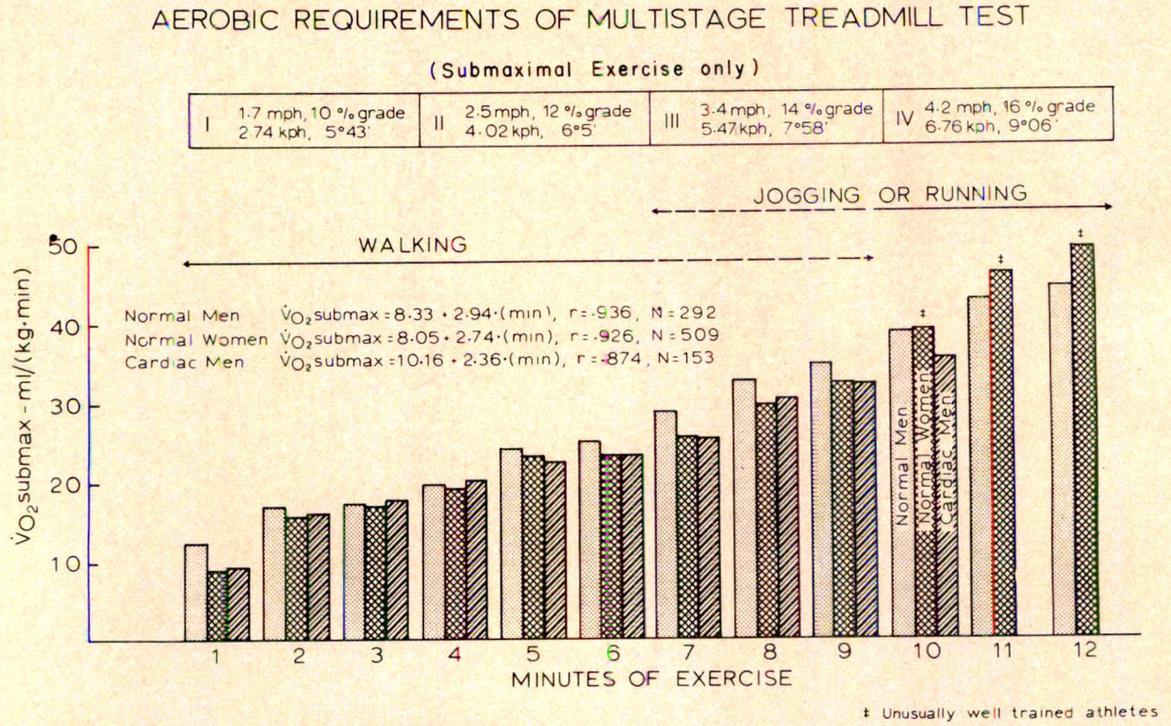

FIGURE 8. Aerobic requirements of healthy middle-aged men and women and men with cardiac disease during submaximal exercise in multistage treadmill test, in absolute values, weight-adjusted. (Reprinted by permission from Bruce et al.[8])

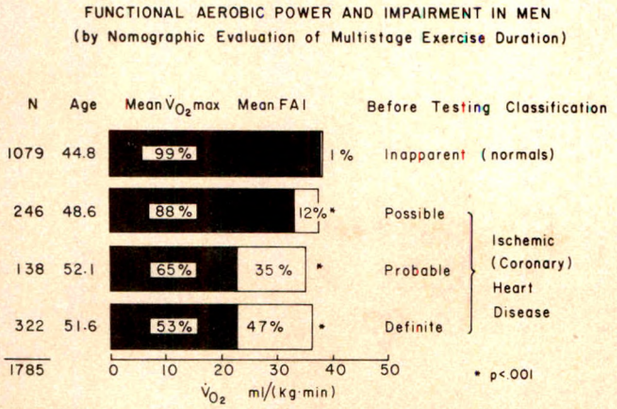

FIGURE 9. Functional aerobic impairment (FAI) and maximal oxygen uptake (VO_2max) in the first 1,785 men in prospective study using multistage exercise treadmill testing. N = number.

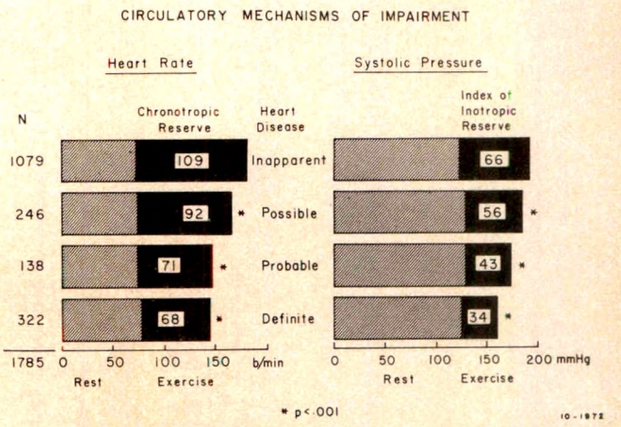

FIGURE 10. Circulatory mechanisms of impairment in thesame 1 men.

appears similar in all ambulatory persons (provided that subjects do not use the handrails for partial support of body weight).[7,8] (Fig. 5). This applies even though there are striking differences in weight-adjusted $\dot{V}O_2$max. Thus, at 1 or 2 minutes before $\dot{V}O_2$max the average percent $\dot{V}O_2$max is similar for normal subjects and patients with heart disease. For the one in five subjects who continue for 1/2 to 1 minute beyond the point of $\dot{V}O_2$max by greater utilization of anaerobic glycolysis for the source of additional energy, $\dot{V}O_2$max is reduced about 3 to 5 percent. Recent unpublished observations of ours indicate that this reduction is due to a further decrease in stroke volume rather than to reductions in either heart rate or arteriovenous oxygen difference.

$\dot{V}O_2$max in liters per minute normally is greater in men than in women (Fig. 6). Accordingly, the relative aerobic costs for a given submaximal exertion are greater in women than in men; they are still greater in men with cardiac disease than in either normal men or normal women, because the weight-adjusted value of $\dot{V}O_2$max is even lower in patients with cardiac disease.

$\dot{V}O_2$max can be increased acutely with nitroglycerin in patients with coronary artery disease but not in normal subjects[9] (Fig. 7). Thus, in the presence of myocardial ischemia, work capacity is enhanced transiently when the preload and afterload imposed on the ischemic myocardium are reduced by peripheral vasodilatation; then the available coronary flow of oxygenated blood is more nearly adequate for the reduced hemodynamic stress applied.

Oxygen costs of isometric work, even when forced to maximal limits, do not approach the values obtained with dynamic exercise. Thus, isometric exertion is useless for testing functional aerobic capacity and does not confer the benefits of endurance training obtained by dynamic exercise conditioning.

Recommended Objectives and Rationale of Testing

The goals of exercise testing should not be restricted to electrocardiographic observations of myocardial ischemia as possible evidence of coronary vascular disease. Instead, the objectives should be to define functional aerobic capacity, the magnitude of its deviation from appropriate normal standards, and the cardiovascular mechanisms of any impairment.

These objectives can be met rapidly, reliably and safely with a multistage treadmill test that encompasses submaximal and maximal exercise.[6] The oxygen requirements for the first four stages or 12 minutes are shown in Figure 8, and average values for maximal oxygen uptake are shown in Figure 6. In meeting these requirements, it is important that none of the body weight be supported by leaning on the handrails; this reduces oxygen requirement and increases variability of measurements of both intensity and duration. In our setting, each subject undergoes a medical examination and a resting electrocardiogram to detect contraindications before testing, and the patient and the electrocardiogram are monitored during and immediately after testing. As a result of these precautions we have observed a morbidity rate of less than 0.1 percent and no mortality in more than 15,000 tests. This experience compares favorably with that of the national experience surveyed by Rockmis and Blackburn,[10] who reported respective morbidity and mortality rates of 2.4 and 1 per 10,000 tests, in a survey of 170,000 exercise tests. Despite these precautions we have witnessed three myocardial infarctions; the first occurred in a clinically normal subject who became acutely ill while taking a hot shower after exercise testing.[11] There also have been three instances of cardiac arrest; in all three, defibrillation was quickly accomplished and myocardial infarction did not occur. Thus, the risk, even to patients with coronary artery disease, is far less than that of coronary arteriography.

With this protocol, $\dot{V}O_2$max and functional aerobic impairment can be derived by regression equations or nomogram from the total duration of exercise.

Clinical Application of Maximal (Treadmill) Exercise Testing

In July 1971, a prospective study of exercise testing was initiated in 15 testing sites in the Seattle area. These included four hospital laboratories, the medi-

cal department in a major industry, and 10 private clinics and offices of physicians and cardiologists. The objectives were to test the hypothesis that persons at risk could be detected earlier and more frequently by maximal exercise testing, and that the mechanisms of clinical events might be predicted in terms of angina or infarction resulting from ischemia, or sudden death from arrhythmia. In the first 16 months, more than 2,200 persons have been tested with only three complications and no mortality.[12] Analysis of the first 1,785 men reveals interesting findings in relation to 1,079 normal subjects and 706 patients classified as having "inapparent" versus "possible," "probable" or "definite" coronary heart disease (Fig. 9). Among the normal subjects, $\dot{V}O_2max$ estimated from the duration of multistage exercise with this treadmill protocol averaged 37 ml/min or 99 percent of expected normal. Accordingly, functional aerobic impairment of only 1 percent represented remarkable validation of the nomographic technique for assessment of functional aerobic capacity. Functional aerobic impairment increased with clinical severity of disease from 12 to 47 percent. Furthermore, determination of the changes in heart rate from the electrocardiogram and changes in systolic blood pressure by sphygmomanometry provided significant insights into the circulatory mechanisms of impairment (Fig. 10). The rate changes averaged 109 beats/min in normal subjects and fell progressively to 92, 71 and 68 beats/min as severity of disease increased. The pressure changes averaged 66 mm Hg in normal subjects and fell with increasing severity of disease to 56, 43 and 34 mm Hg. The former represents the chronotropic reserve, and the latter an index of inotropic reserve of the left ventricle. Actually, since peripheral vascular resistance diminishes markedly with maximal exercise, the change in pressure underestimates the inotropic reserve of the ventricle.

In conclusion, some of the salient principles of exercise testing of ambulatory normal subjects and patients with heart disease have been reviewed briefly. Isometric exercise may be hazardous; dynamic exercise offers greater benefits and fewer risks. Experience with the multistage treadmill test indicates that it is a practical, reliable and safe method of testing, with the distinct advantage that its use permits definition of the functional capacity of the cardiovascular system.

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Exercise Electrocardiography: Recognition of the Ischemic Response, False Positive and Negative Patterns

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The ischemic electrocardiographic response is characterized by S–T segment depression in the left ventricular leads. When this response is elicited by exercise and is accompanied by anginal discomfort, it constitutes powerful diagnostic evidence of the presence of coronary arterial obstructive disease. The amount of exercise required to elicit the response is closely related to the extent of the obstruction. S–T segment elevation provoked by exercise rarely occurs with proximal severe stenosis in the left anterior descending coronary artery or in leads exploring the region of healed myocardial infarcts. Depression of the J point may be an ischemic manifestation reversible by administration of nitroglycerin.

The ischemic electrocardiographic response may be obscured by conduction defects as in bundle branch block and healed myocardial infarcts. False positive ischemic responses may be encountered in patients taking digitalis glycosides or potassium-depleting drugs, or in patients with hyperadrenergic states, pectus excavatum or short P–R intervals.

Depression of the S–T segment has been recognized as the electrocardiographic hallmark of myocardial ischemia since Feil and Segal[1] recognized its association with angina pectoris in their classic observations published in 1928. They observed a man with a normal resting electrocardiogram who had a spontaneous attack of angina while an electrocardiogram was being taken. The tracing they recorded resembled that of Figure 1, which represents the sequential electrocardiographic changes seen in one of our patients who experienced an anginal attack, probably attributable to anxiety, as the tracing was being recorded. Depression of the S–T segment with a horizontal configuration coincided with the development of anginal pain similar to the pain he customarily had during physical exertion. Relief of pain after sublingual administration of nitroglycerin was associated with return of the S–T segment to the base line. This sequence of events with the association of angina and depressed S–T segment, both reversed by the administration of nitroglycerin, constitutes very strong evidence, perhaps even proof, that the S–T segment depression was due to myocardial ischemia.

The impracticality of obtaining electrocardiographic monitoring of naturally occurring anginal attacks has led to the development of provocative tests among which the two-step test of Master[2] is the only one to have survived into the present era. This test, considered a single stage test since the work load remains constant throughout the duration of the exercise period, has been supplanted in our institution in recent years by a multistage treadmill exercise test.[3] The idea underlying multistage testing is that one can begin by subjecting a patient to a low level of work load not in excess of what he is customarily able to do without distress. The work load can then be increased in small increments during continuous electrocardiographic monitor-

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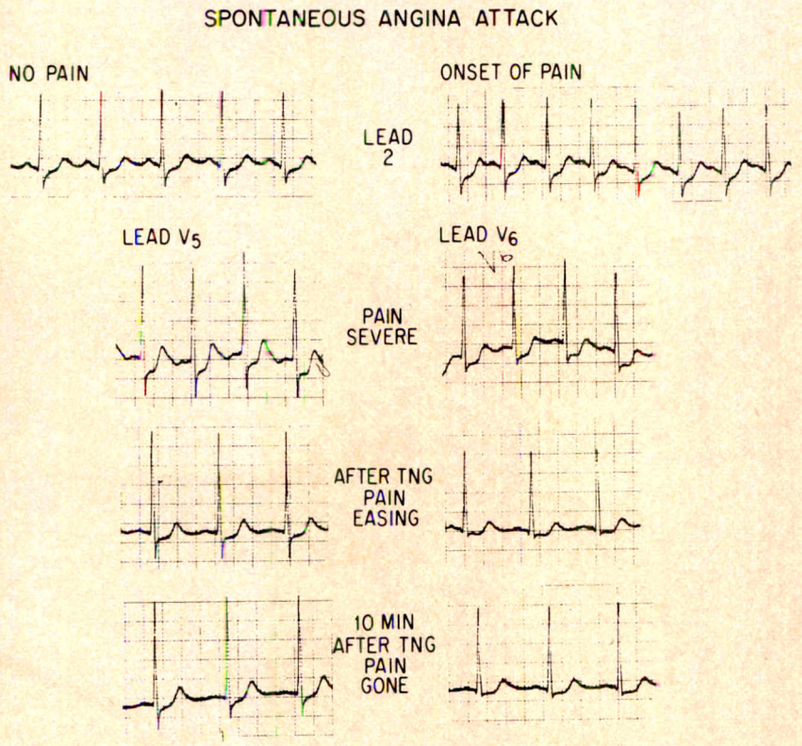

FIGURE 1. Electrocardiograms recorded during development of a spontaneous anginal attack and during its relief by administration of sublingual nitroglycerin (TNG). The fully developed ischemic response of horizontal depression of S–T segments is seen during the height of the attack in lead V_6.

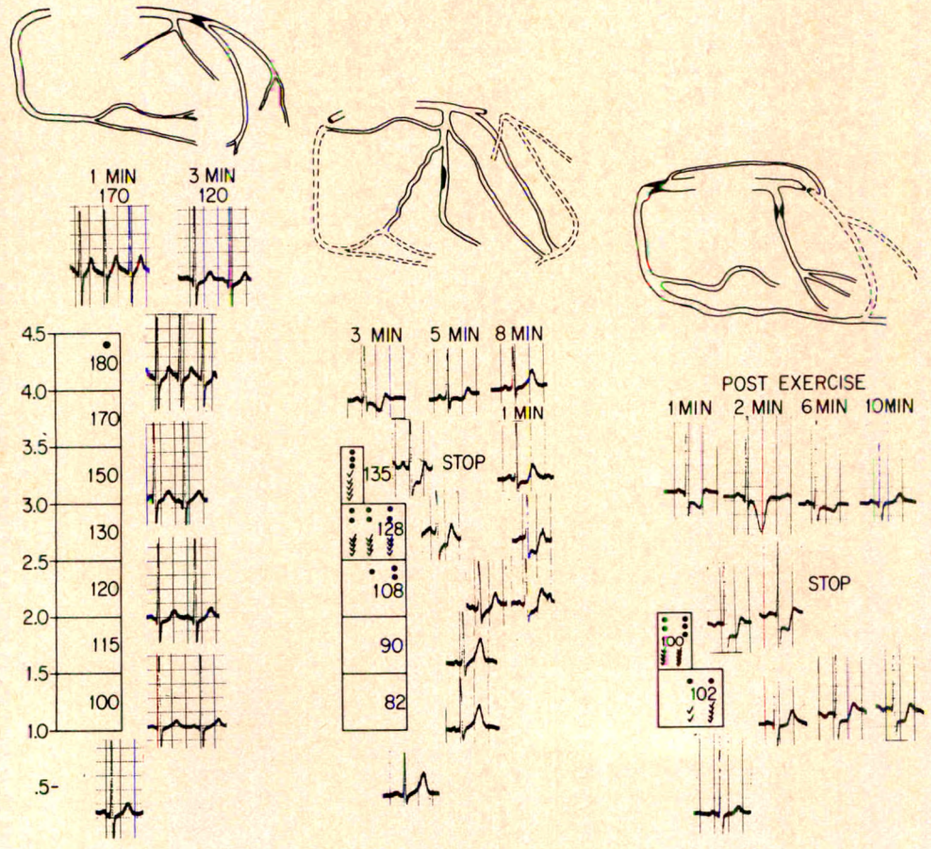

FIGURE 2. Three examples of standard treadmill tests showing diagrammatic representation of the test with each block representing 3 minutes of walking at 10 percent grade at the speed in miles/hour indicated by the top of the block. Maximal heart rate for each stage is inside each block. Dots at top of blocks indicate the severity of angina. The checks at bottom of blocks indicate millimeters of S–T segment depression. Electrocardiographic strips for appropriate stages are mounted to the right of the block diagrams. Sketches of coronary arterial anatomy as determined from coronary angiograms are above. **Dotted lines** indicate vessels filled by collateral vessels beyond the area of obstruction. Nonischemic response is shown on the left, ischemic responses in the center and on the right.

ing until ischemic manifestations in the form of anginal discomfort or S–T segment deviations, or both, make their appearance. In this way the work load imposed is tailored to the capacity of the patient and diagnostic accuracy is enhanced. Our test is designed to go beyond diagnostic capability to the determination of the patient's exercise tolerance as limited by the symptomatic manifestations of the disease—anginal pain, dyspnea, fatigue or leg pain. For this purpose, exercise is continued until the patient reaches a symptomatic end point score of 3+, indicating symptoms of moderately severe intensity (in our scoring system 1+ indicates mild, 2+ moderate, 3+ moderately severe and 4+ maximally severe intensity). This stopping point provides a tolerance test of good reproducibility that is useful for following up the course of the disease and the effects of therapeutic intervention, drugs, surgery or exercise training.[4]

Intelligent use of exercise testing of any type requires an understanding of the behavior of the electrocardiogram as it is influenced by exercise, recognition of the ischemic response, appreciation of the false positive and false negative response as well as the effects of certain electrocardiographic patterns that might distort the results.

The Ischemic Response

Figure 2 illustrates three treadmill tests performed in our laboratory. The graphic scheme representing the sequential stages is accompanied by (1) electrocardiographic strips obtained with use of a bipolar transthoracic lead showing the patterns at various stages, and (2) drawings of the coronary arterial anatomy as disclosed by coronary cineangiograms. In the case illustrated on the left, exercise performance was normal, and there were no anginal symptoms or ischemic manifestations in the electrocardiogram. This patient had previously demonstrated Prinzmetal's variant angina[5] with nocturnal episodes of pain and S–T segment changes as well as mild angina at the 4 miles/hour stage of the treadmill test. The normal response illustrated occurred after 1 year of daily walking exercise. The local stenotic lesions in the left anterior descending coronary artery remained the same upon repeat study. Completion of the 4 or 4.5 miles/hour stage of the test at 10 percent upgrade represents a performance equal to a maximal effort for the average sedentary adult American man. No deviation of the T waves or S–T segments occurred either during or after exercise in this high work load test.

The center panel of Figure 2 illustrates an ischemic response in a man who has achieved an improvement of capacity during a program of daily walking exercise. He was stopped by 3+ angina at the 3.5 miles/hour stage. Ischemic depression of the S–T segment appears coincident with the onset of anginal distress, and the degree of depression increases as the intensity of the pain builds up to the 3+ end point. The postexercise recovery period is associated with deep T wave inversion and then gradual return to the normal pattern. The arteriogram demonstrated total

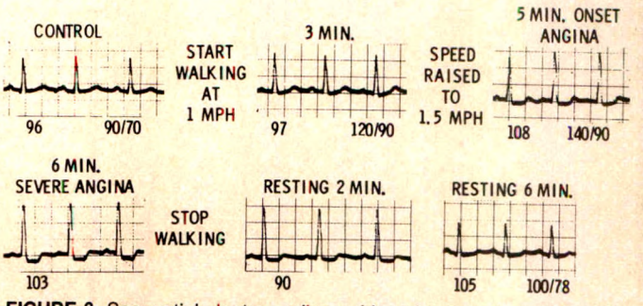

FIGURE 3. Sequential electrocardiographic strips from treadmill test of a patient with severe angina, poor exercise tolerance and extensive three vessel coronary obstructive disease. MPH = miles/hour.

occlusions in both the left anterior descending and the right coronary arteries with collateral filling beyond the occlusions. Severely ischemic S–T depression is usually seen over areas of myocardium supplied primarily by collateral circulation.

The third panel of Figure 2 illustrates a poor performance by a severely disabled man who was halted by 3+ angina in the second stage of the test at a low work level. Very severe ischemic depression is seen during exercise and very marked T inversion is seen during the recovery period. Total occlusion of the left anterior descending artery and severe stenoses in the left circumflex and right coronary arteries reduced coronary perfusion to all parts of the heart.

The ischemic electrocardiographic responses shown in Figure 2 represent advanced and unmistakable changes. One cannot expect to find such typical changes in all cases, nor can one expect to find consistent relations between the degree of S–T segment depression and the intensity of anginal symptoms or the extent of impaired coronary perfusion. For example, the patient whose electrocardiograms are shown in Figure 3 had such severe anginal pain at a low working level that he could not progress beyond the 1.5 miles/hour stage of the standard treadmill test. With severe pain there was only 1 mm of horizontal S–T segment depression and no T wave inversion in the postexercise recovery period. His coronary angiogram showed total occlusion of the right coronary artery with collateral filling distally, total occlusion of the left circumflex artery with preservation of a large marginal branch and severe stenosis in the proximal left anterior descending system—advanced three vessel disease yet minimal electrocardiographic changes provoked by exercise.

The ischemic response is not always manifested by S–T segment depression. Figure 4 displays electrocardiographic strips from an exercise test in which the angina was accompanied by marked S–T segment elevation. This response occurred in a man whose only coronary arterial lesion was a single high grade stenosis in the proximal left anterior descending coronary artery. The pattern must be very rare because we have seen it only a few times, mostly in persons who have had a prior myocardial infarction. This patient had never had an infarct.

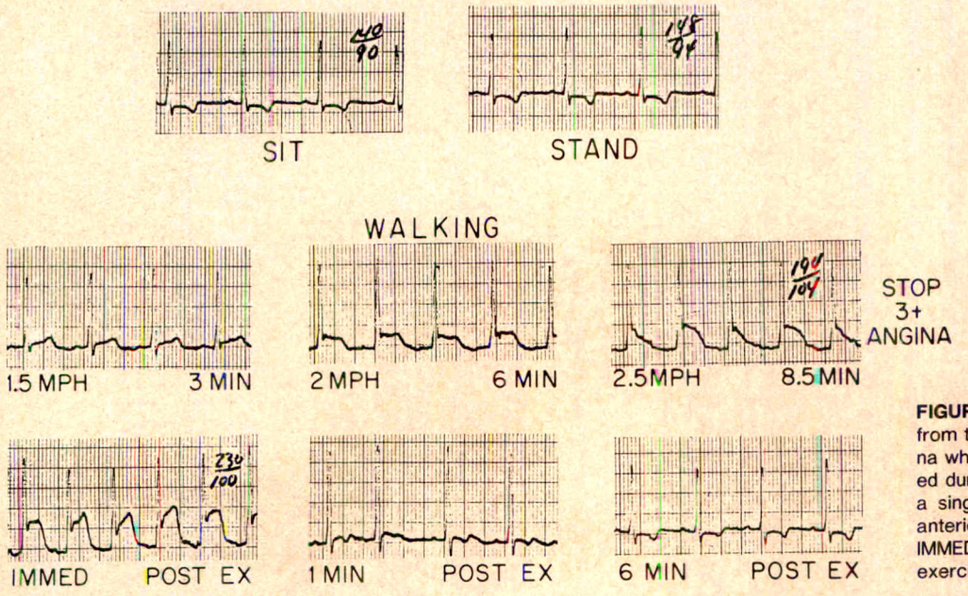

FIGURE 4. Electrocardiographic strips from treadmill test of a patient with angina whose S–T segments became elevated during pain. Ischemia was caused by a single high grade stenosis of the left anterior descending coronary artery. IMMED = immediately; POST EX = post-exercise.

The Problem of J Point Depression

The development of junctional or J point depression with the S–T segment remaining in an upward slanting orientation frequently causes uncertainty in interpretation of exercise electrocardiograms. This finding in the large series of subjects with long-term follow-up reported by Robb and Marks[6] was not associated with an increased prevalence of coronary events and thus has been regarded by many as a non-ischemic or perhaps innocent electrocardiographic manifestation. In our experience, J point depression is often a stage in the development of the ischemic response. Figure 5 illustrates two treadmill tests performed 3 months apart. In the first test the patient was stopped at the 3.5 miles/hour stage by fatigue, but he was experiencing mild substernal heaviness. In the second test, performed after a 10 lb weight loss and a program of a daily walking exercise, the pattern of J point depression finally evolved into a clearly ischemic pattern as the S–T segment became horizontal in the 4 miles/hour stage and he was stopped by dyspnea and angina. The ischemic pattern persisted into the postexercise recovery period. Cause of the ischemia was a high grade stenosis of the left main

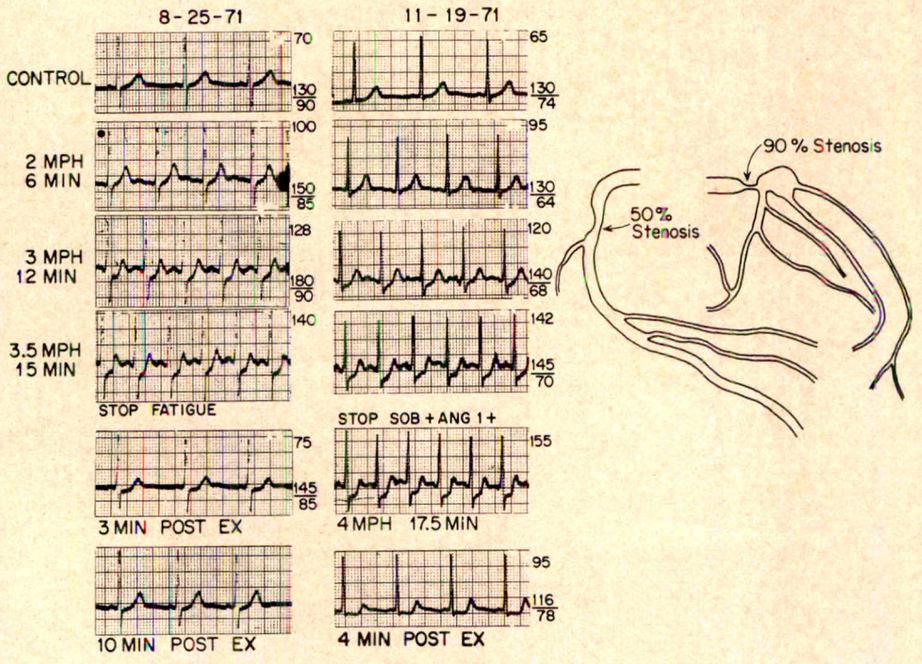

FIGURE 5. Two treadmill tests 3 months apart performed by a patient with mild angina. The first test resulted only in J point depression, but the second test yielded a classic ischemic response. Coronary angiograms disclosed high grade stenosis of the left main coronary artery. ANG = angina; SOB = shortness of breath.

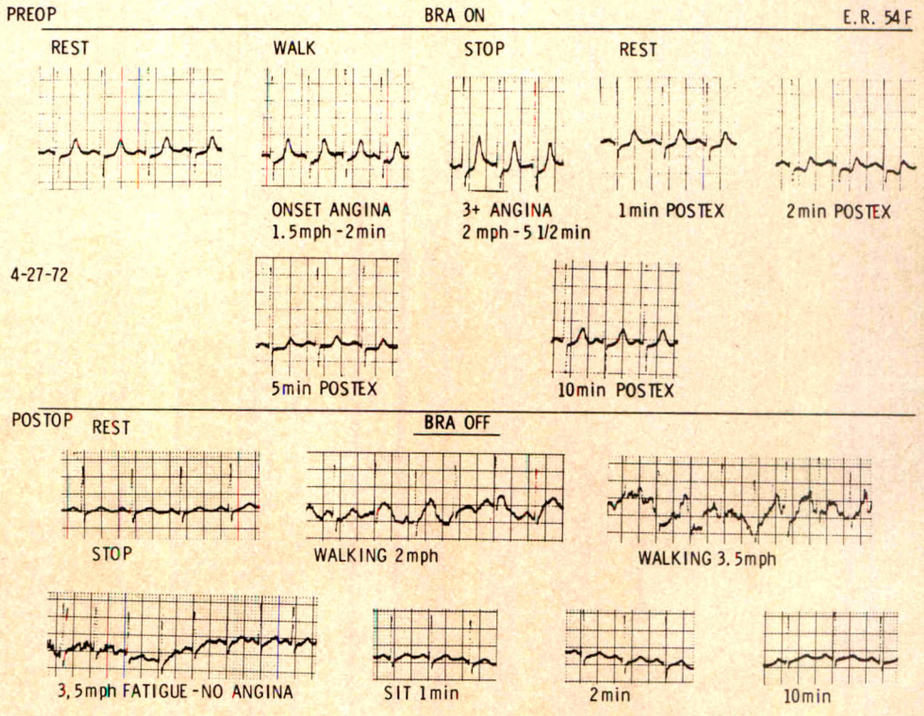

FIGURE 6. Electrocardiographic strips from two treadmill tests performed by a patient who had a good result from a saphenous vein bypass graft operation. In the preoperative test **(top)** the ischemic response emerges in the postexercise period. The postoperative test **(bottom)** demonstrates improved capacity and absence of ischemia, but the tracing is marred by motion artefact caused by uncontrolled motion of the bosom.

coronary artery proximal to an aneurysmal poststenotic dilatation.

In some instances we have been able to confirm the ischemic origin of J point depression by sublingual administration of nitroglycerin to the patient during treadmill walking and by observing the regression of this electrocardiographic pattern and disappearance of angina as walking continued at a steady pace. Thus, J point depression may indeed be a manifestation of myocardial ischemia, but it cannot be interpreted with reliability unless confirmatory evidence can be generated: the presence of typical anginal distress, the eventual emergence of the typical ischemic pattern either during or after exercise, or the demonstrated presence of significant coronary arterial obstruction.

Postexercise Ischemic Pattern

Ischemic S–T depression sometimes emerges only in the recovery period after exercise. The top panel of Figure 6 shows the sequential electrocardiographic changes during and after a standard treadmill test of a 54 year old woman who was stopped at the 2 miles/hour stage with 3+ angina. J point depression present at the end of exercise evolved into a clearly ischemic downslanting depression in the postexercise period, leaving no doubt about the ischemic nature of the response. Figure 6 also illustrates two other points. One is that treadmill testing is useful for assessing the results of coronary artery bypass graft surgery. The test at the bottom was conducted 3 months after a single saphenous vein graft bypassing a high grade stenosis in the left circumflex coronary artery. Great improvement in exercise tolerance is shown by completion of the 3.5 miles/hour stage of the test without ischemic manifestations. The second is that an important technology enters into the recording of adequate electrocardiographic tracings during exercise. The extensive low-frequency motion artefact seen in the lower record occurred because the patient was not wearing a brassiere on the day of that test. Motion of the bosom during brisk walking causes pulling and tugging of the skin to which the electrode at the V_5 position is attached. Use of a brassiere usually avoids this form of motion artefact, as in the top record. Detailed instructions for placement and fixation of electrodes to obtain optimal recording fidelity have recently been published by the American Heart Association.[7]

In some patients with a severe ischemic response to exercise, the postexercise period is characterized by marked bradycardia. In Figure 7 a strong vagal influence is suggested by a series of junctional escape beats before the return of slow sinus rhythm and then a gradual reversion to a normal rate. The vast majority of bradycardic responses do not progress to this extreme degree of slowing.

A rare cause of postexercise bradycardia is the development of atrioventricular block. The patient whose electrocardiogram is shown at the bottom of Figure 7 had first degree heart block during exercise with progressive P–R prolongation in the postexercise period eventually leading to a brief episode of Wenckebach mechanism followed by recovery.

The Abnormal Resting Electrocardiogram

When a T wave inverted in the resting electrocardiogram becomes upright during exercise-induced

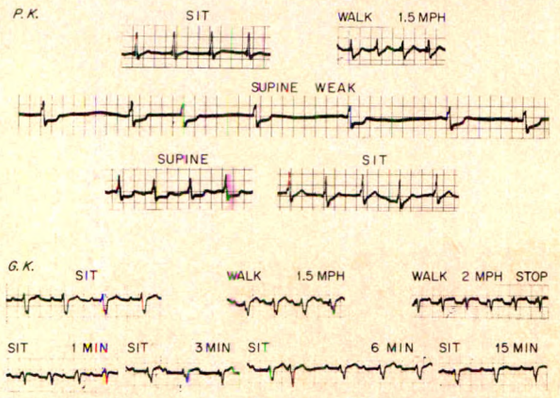

FIGURE 7. Electrocardiographic strips from treadmill tests performed by two subjects, one **(top)** demonstrating marked bradycardia in the postexercise period and the other **(bottom)** with first and second degree heart block.

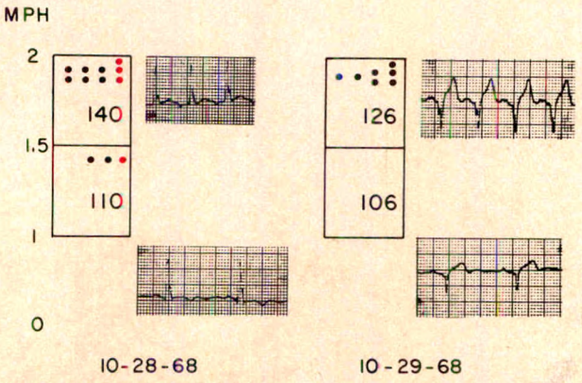

FIGURE 8. Treadmill test results of a man with angina and prior myocardial infarction whose inverted T wave became upright in lead V_5 during angina **(left)** and whose S–T segment became markedly elevated over the area of the infarction in lead V_2 **(right).** (Reprinted by permission from Kattus and MacAlpin.[8])

angina the question arises whether this reversal of T wave polarity represents an ischemic response. The problem is illustrated in Figure 8 in which the electrocardiogram of a patient with severe angina and an old anteroseptal myocardial infarct demonstrated a negative T wave in lead V_5 which became upright when the patient was stopped by 3+ angina. On the next day when the monitoring electrode was placed at the V_3 position, the site of the QS complex from the old infarct, striking S–T segment elevation was found at the time of 3+ angina. It was thus concluded that the strong influence of the repolarization potentials seen over the area of infarction were also influencing the surrounding areas. The significance of the S–T segment elevation is not entirely clear. We have seen it in patients after infarction even though they have no symptoms with vigorous exercise. We believe that this response does not in itself indicate myocardial ischemia but is an electrical consequence of the physical forces that occur at the boundary between scar tissue and contracting myocardium as though there were a temporary ventricular aneurysm during exercise at the site of the healed infarct. Thus, reversal of T wave polarity near the site of an old infarct cannot be regarded as reliable evidence of myocardial ischemia.

The series of tests recorded in a man with angina and a healed anteroseptal myocardial infarct (Fig. 9) illustrate another perplexing problem. With all tests conducted using the same electrocardiographic lead system (negative electrode at RV_6 position and positive electrode at V_5) there was initially S–T segment depression with the occurrence of 3+ angina. Four months later after an exercise training program there was slight improvement of exercise tolerance, but the S–T segment was elevated when 3+ angina occurred.

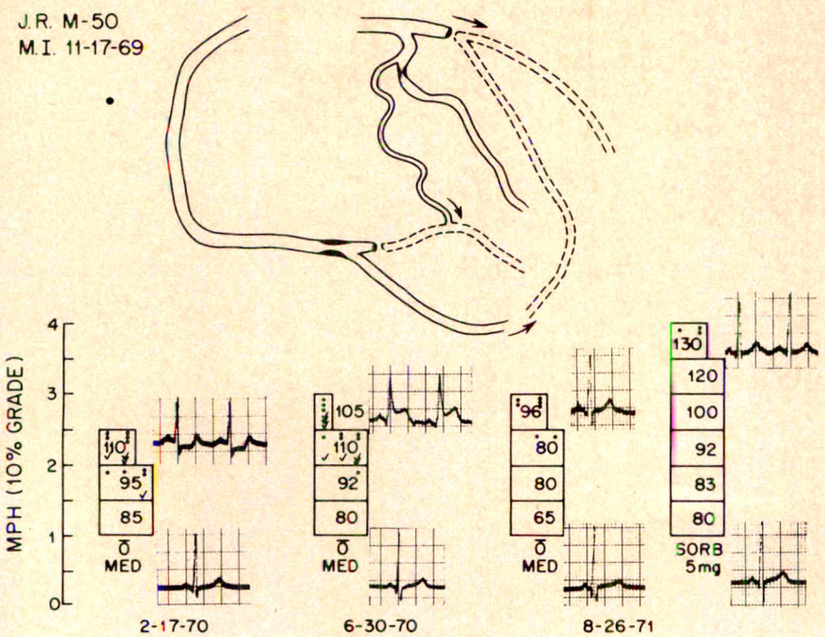

FIGURE 9. Sketch of coronary arterial anatomy **(top)** and sequential treadmill tests performed by a 50 year old man with residual angina after an anteroseptal myocardial infarction in November 1969. In the first test, the S–T segment is depressed; in the second test it is elevated; in subsequent tests, it is unchanged. Ō MED = no medication; SORB = premedication with isosorbide dinitrate.

On the third test, the S–T segment was unchanged with the same intensity of angina, and was also unchanged on a fourth test, when the patient had a greatly improved performance under the influence of isosorbide dinitrate absorbed from the buccal membrane. These findings suggest that the influence of S–T segment elevation from the region of the healed infarct may have dominated the second test, whereas the subendocardial ischemia of the noninfarcted muscle may have dominated the first. In the third and fourth tests the two influences may have canceled out each other. It must be concluded that interruption of the normal pathways of depolarization as in myocardial infarction lead to abnormal pathways of repolarization; these alterations may distort the display of S–T segment changes during ischemia, thus rendering them uninterpretable.

Bundle Branch Block

Distortion of the repolarization pathway in bundle branch block may obscure the ischemic response or produce a deflection that resembles ischemia but is not. Figure 10 shows the development and regression of a rate-related left bundle branch block in an asymptomatic man who has excellent exercise tolerance, normal ventricular contractility and widely open coronary arteries. During exercise the S–T seg-

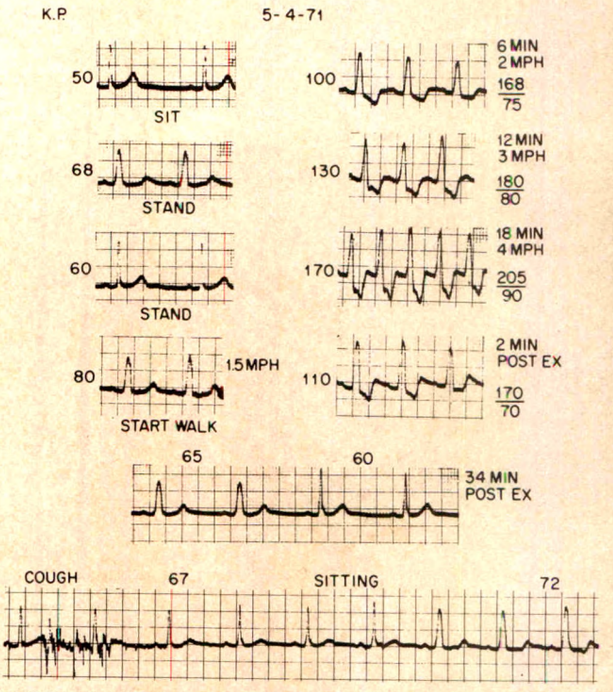

FIGURE 10. Electrocardiographic strips from a treadmill test performed by an asymptomatic man with rate-related left bundle branch block. He has good exercise tolerance and no coronary arterial obstruction.

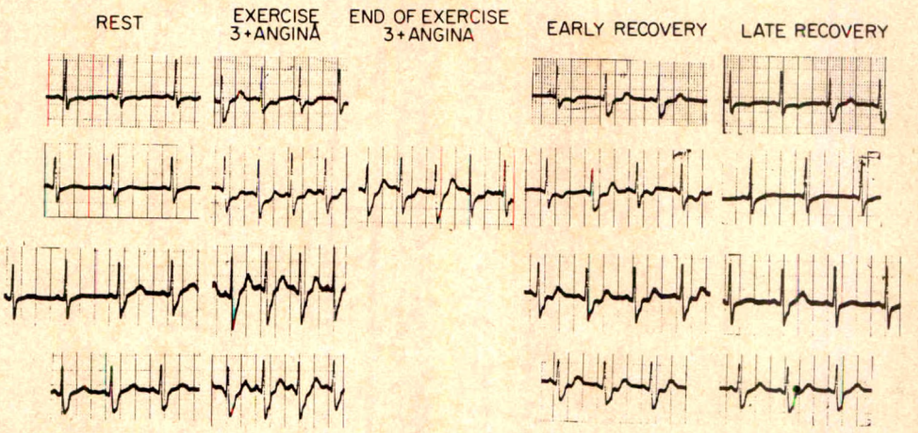

FIGURE 11. Electrocardiographic strips from four treadmill tests performed over a 2 year period by a man with severe angina and intermittent right bundle branch block which is at first exercise-induced but later becomes established. The ischemic response is readily seen in normally conducted beats but is obscured in the beats with bundle branch block.

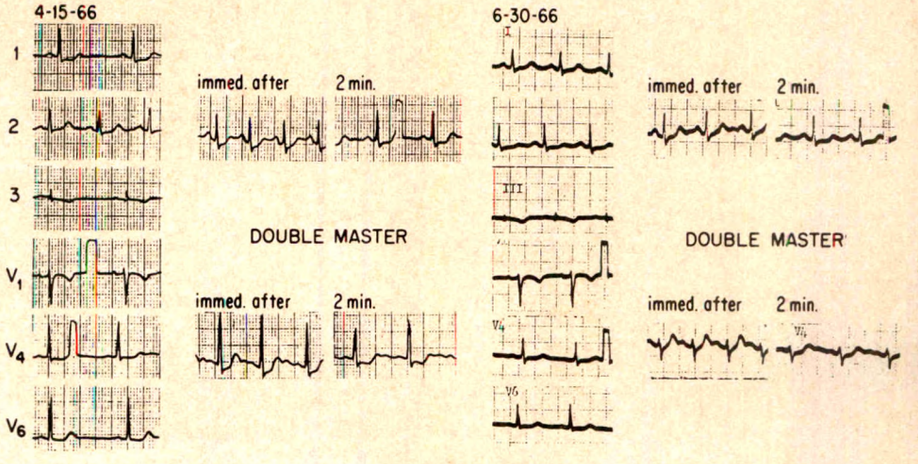

FIGURE 12. Electrocardiographic strips from double Master tests performed by a young woman at first when she was taking digitalis-containing reducing pills and again when she had discontinued these pills for 2 months. (Reprinted by permission from Kattus et al.[10])

ments are deeply depressed, but this alteration is due not to ischemia but to the abnormal pathway of repolarization secondary to the aberrant activation pathway.

Right bundle branch block also alters repolarization and thereby may obscure the ischemic effect on the S–T segment. In Figure 11 a sequence of treadmill runs shows intermittent right bundle branch block finally evolving into fixed right bundle branch block. During the period of intermittency the ischemic pattern provoked by exercise can be seen in the normally conducted beats but not in the bundle branch blocked beats. Later downslanting of the S–T segments is seen in the postexercise segments, but the classic ischemic pattern formerly present has been obscured by the conduction defect.

False Positive Ischemic Responses

Drug effects: S–T segment depressions closely resembling the ischemic pattern but not caused by ischemia have been recognized. Among the most common are those due to drug therapy. Digitalis glycosides may produce a pattern[9] such as that seen in Figure 12. On the left of the illustration are a resting electrocardiogram and strips from a double Master test in which an ischemic pattern was found. The tracings are from a 21 year old healthy woman who had been taking weight-reducing pills, among which one turned out to be digitalis presumably given for its anorectic effect. A repeat two-step test performed 2 months after discontinuation of the drug yielded a normal response.

The studies shown in Figure 13 were performed in a young physician who had experienced an episode of sharp stabbing chest pain. The dramatic postexercise ST–T wave inversions were not associated with discomfort. The rounded configuration of the trough of the inverted T wave resembled the pattern of digitalis effect. The patient denied taking digitalis but admitted that he had been treating himself for mild hypertension with reserpine and chlorothiazide. Several weeks after he stopped taking these agents, a normal exercise performance was elicited. It is believed that some degree of potassium depletion was responsible for the unusual T wave pattern that emerged in the postexercise electrocardiogram.

Vasoregulatory asthenia: A pattern that we have encountered at least three or four times a year is one that has often led to erroneous diagnoses of coronary artery disease. Holmgren et al.[11] in Sweden have called it the syndrome of vasoregulatory asthenia. Its features are illustrated in Figure 14. The patient usually complains of ill-defined chest pains not well correlated with exertion and not usually convincing evidence of angina. The electrocardiogram often manifests S–T sagging or T wave inversion when the patient stands up. With exercise there is usually an inappropriate acceleration of the heart rate at low work levels, and the S–T segments become depressed as in Figure 14. These changes are abolished or drastically modified by beta adrenergic blockade induced by propranolol. They may be entirely abolished by a period of mild exercise training such as walking 2 miles every day. Coronary arteriograms in patients with these findings disclose no obstructive disease in the blood vessels. The syndrome is believed to be due to excess adrenergic drive or perhaps excess responsiveness to adrenergic influence. In our experience it has

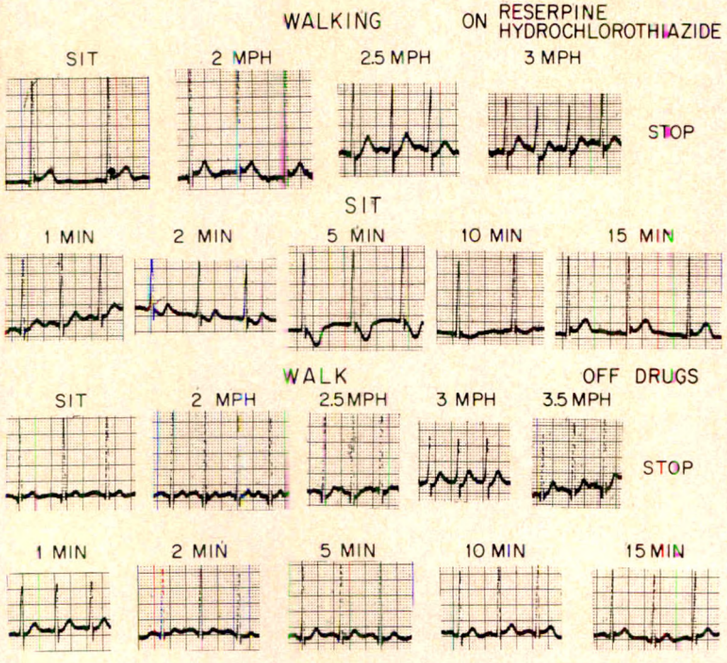

FIGURE 13. Electrocardiographic strips from treadmill tests performed by a young man who was taking reserpine and chlorothiazide during the first run and had discontinued these drugs for 2 months at the time of the second run.

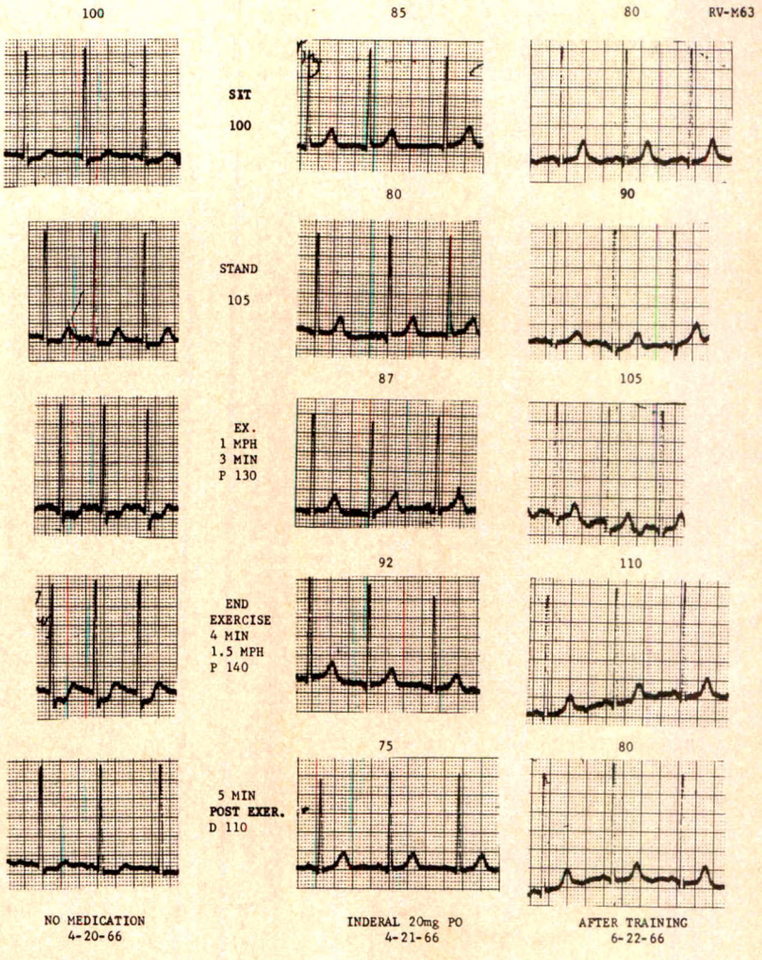

FIGURE 14. Electrocardiographic strips from three treadmill tests performed by a 63 year old man who was stopped by leg claudication pain at a low work level but who had no anginal pain. During the first run, the patient was taking no medication. The second test was performed after oral administration of 20 mg of propranolol (Inderal®) and the third after 2 months of a daily walking program of 1.5 miles/day performed in stages as permitted by leg pain. The changes in the first test are attributed to vasoregulatory asthenia. P and D = pulse rate. (Reprinted by permission from Kattus et al.[12])

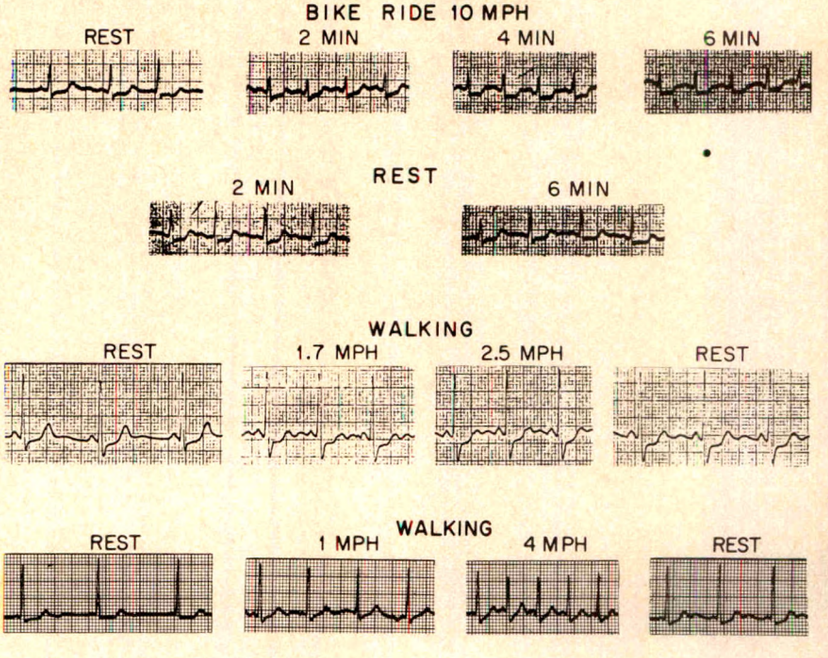

FIGURE 15. Top, electrocardiographic strips recorded before, during and after bicycle exercise in a patient who did not have pain during the test but stopped because of fatigue. She had marked pectus excavatum. **Bottom,** two treadmill tests performed by a patient with a short P–R interval. The first test was conducted with the negative electrode on the manubrium and the positive electrode at the V_5 position. During the second test, the negative electrode was in the right axilla.

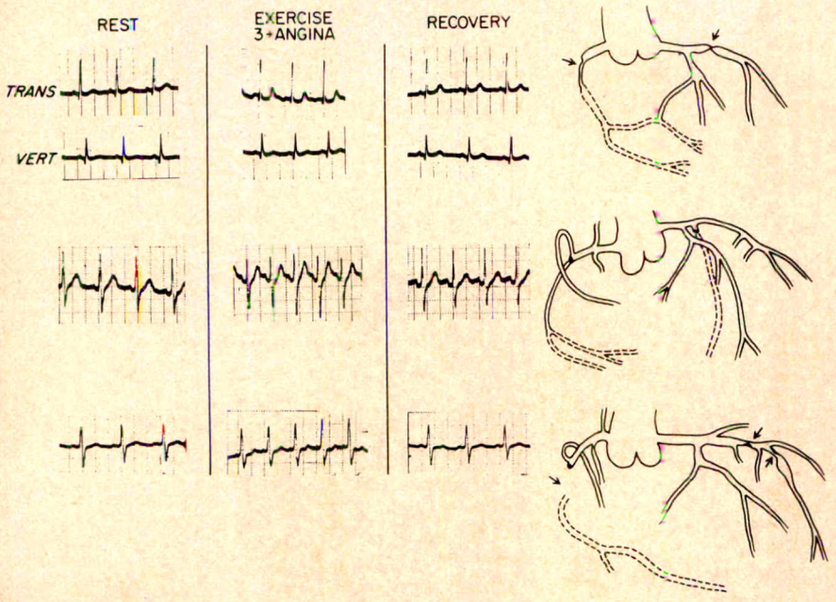

FIGURE 16. Electrocardiographic strips from treadmill tests performed by three patients who had no S–T segment shifts during 3+ angina. Transthoracic leads were recorded in all, and the first also had a vertical lead. All three subjects had prior inferior myocardial infarction. Sketches of the coronary arterial anatomy are at right.

a good prognosis, and we have never known a coronary event to occur in such a patient.[12]

Chest deformity: Two uncommon causes for false positive electrocardiographic responses to exercise are shown in Figure 15. At the top are strips from a bicycle exercise test in a woman who had vague chest pain. No pain was elicited during the test, and the S–T segment depression found was essentially similar before and after the exercise. Angiograms revealed normal coronary arteries. We believe her electrocardiographic pattern was due to a marked pectus excavatum. We have seen three other patients with this chest deformity who had similar electrocardiographic findings with exercise testing.

Effects of atrial potentials: The lower panel of Figure 15 represents a false positive test due to the effect of the atrial repolarization wave on the S–T segment. The patient, an asymptomatic woman, has a short P–R interval of 0.11 second. In the first test the monitored electrocardiographic lead has the negative electrode on the manubrium and the positive electrode at the V_5 position. This lead is aligned along the axis of the P wave and tends to amplify the effects of the atrial potentials. Thus, the S–T depressions associated with the amplified TA wave led to the appearance of an ischemic response. When the negative electrode was placed in the right axillary line, the lead axis became more perpendicular to the P wave axis and the influence of the TA wave was greatly lessened in this patient with the Lown-Ganong-Levine syndrome.[13]

False Negative Responses

False negative electrocardiographic responses occur in about 10 percent of subjects who undergo testing. These patients have typical anginal distress during exercise without an accompanying pattern of ischemia on the electrocardiogram. The vast majority of these responses are found in subjects who have survived prior myocardial infarction. The tracings in Figure 16 are from three such subjects, all of whom had old healed inferior myocardial infarcts and Q waves in leads II, III and aVF but normal findings in the precordial leads. None of these patients had S–T segment deviation during exercise-induced 3+ angina. In each case multiple lead positioning did not reveal the expected changes. The coronary angiograms of these patients suggested that the angina was due to ischemia of the anterior myocardial wall since each had obstructive disease in the left anterior descending coronary system in addition to the total occlusion of the right coronary artery that had produced the previous infarcts. The reason for the failure of the ischemic electrocardiographic pattern to emerge is not apparent, but the typical character of the anginal pain, its relation to exercise and its response to nitroglycerin left no doubt about its ischemic origin. Thus in such cases when the presence of myocardial ischemia is clearly defined by other means including the resting electrocardiogram and arteriogram the classic ischemic electrocardiographic pattern is not a necessary component of a valid exercise test for exercise tolerance. In this situation the anginal symptom can be taken at face value even though the electrocardiographic proof is lacking.

Conclusion

This discussion has been concerned with the recognition of ischemic electrocardiographic responses as they are elicited by exercise testing under controlled conditions. Such changes have to do with the form of the depolarization and repolarization phases of the cardiac action potentials. The extensive problem of cardiac dysrhythmias as they are provoked by exer-

cise have been purposely avoided since another paper appearing in this Symposium is concerned with this subject.

The conclusions that may be drawn are (1) that the exercise electrocardiogram must be continuously monitored during testing since changes may be expected from moment to moment, and (2) that good fidelity of recording must be assured by careful attention to electrode placement and fixation to avoid motion and positional artefacts. When properly obtained, the exercise electrocardiogram is a powerful diagnostic tool for identifying myocardial ischemia and assessing its severity. Accurate interpretation of the results demands an awareness of the variations of patterns that might be expected, the possibilities of false positive and false negative responses and the misleading effects of pharmacologic and metabolic influences.

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Disturbances of Cardiac Rhythm and Conduction Induced by Exercise

Diagnostic, Prognostic and Therapeutic Implications

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Alterations of cardiac rhythm and conduction occur frequently during exercise stress testing and may provide significant information regarding cardiovascular status. Exertion may induce arrhythmias as a result of sympathetically enhanced phase 4 depolarization of ectopic foci or the induction of myocardial ischemia secondary to increased myocardial oxygen demand. Exercise may abolish arrhythmias present in the resting state, an effect attributed to overdrive suppression and inhibition related to sinus tachycardia. Although a wide spectrum of electrophysiologic changes may be elicited by stress testing, ventricular dysrhythmias are of primary importance. Premature ventricular contractions that are frequent, multifocal, repetitive or associated with light work loads have been particularly indicative of coronary artery disease. Exertional ventricular irritability has been observed more frequently in patients with coronary atherosclerosis involving two or more coronary vessels and accompanied by abnormalities of left ventricular wall motion. Exercise testing may have advantages over portable monitoring in the detection of ventricular arrhythmias. The mere presence of ventricular ectopic beats at rest does not preclude carefully performed graduated stress testing nor does their disappearance during effort exclude the presence of coronary artery disease.

Disturbances of cardiac rhythm and conduction are commonly observed during exercise stress testing and may provide important clinical information on cardiovascular status. Thus, exertion-induced ectopic ventricular rhythms may be of diagnostic,[1,2] prognostic[3] and therapeutic[4] significance in coronary artery disease. In addition, exercise stress testing has been utilized to evaluate the role of arrhythmias in patients with syncopal episodes and to assess the efficacy of antiarrhythmic therapy.[5] In this paper we review current knowledge of the electrophysiologic response of the heart to physical exertion and examine directions for future investigation.

Electrophysiologic Effects of Exercise

Exercise is capable of inducing a number of alterations in the electrical activity of the myocardium, the net result of which may be either enhancement or inhibition of ectopic rhythms and abnormal conduction. Derangement of cardiac electrophysiology as a response to exercise is unpredictable in an individual subject, and cardiac rhythm and conduction may vary as a function of the level of exertion or stress. Figure 1 illustrates physiologic alterations accompanying exercise and their possible sequelae.

Pathophysiologic basis for arrhythmias during exercise: The stress of exertion frequently results in the appearance of arrhythmias not present in the resting state. The production of such arrhythmias by exercise has been attributed to heightened sympathetic tone, increased myocardial oxygen demand, or a combination of these fac-

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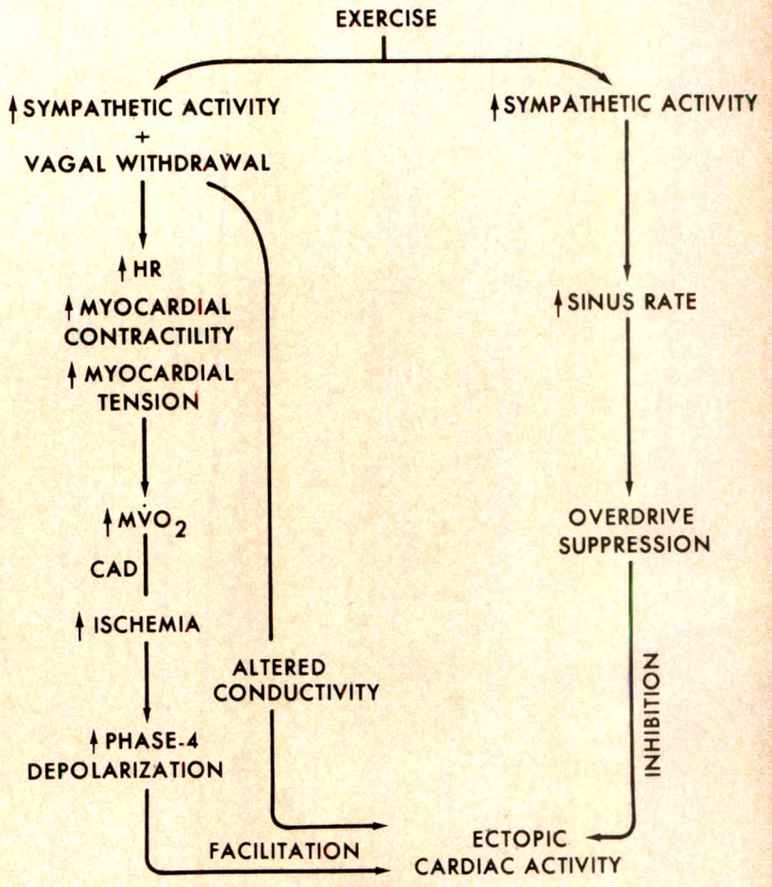

FIGURE 1. Physiologic alterations accompanying exercise. ↑ = increased; ↓ = decreased; → = unchanged.

tors. Augmented sympathetic drive to the myocardium may provoke ectopic Purkinje pacemaker activity by accelerating the rate of phase 4 depolarization at this site, enhancing its spontaneous discharge and thereby increasing automaticity.[6,7] Increased myocardial oxygen demand, when not matched by oxygen supply, results in local tissue hypoxia. Myocardial hypoxia produces temporal dispersion of depolarization and repolarization as well as alterations in conduction velocity and thereby provides an ideal substrate for the appearance of arrhythmias related to both automaticity and reentry.[8] Thus, myocardial ischemia may act as the stimulus for the appearance of abnormalities of rhythm and conduction during stress testing.

Myocardial ischemia is a common response to exercise stress in the presence of coronary artery disease. Myocardial oxygen consumption ($M\dot{V}O_2$) is determined by heart rate, contractility and intramyocardial tension.[9] The effect of exercise upon these factors augments $M\dot{V}O_2$ and thus may result in myocardial ischemia if oxygen demand exceeds supply. This disparity is usually a consequence of the restricted flow reserve of the coronary circulation in coronary atherosclerotic disease. Such an imbalance may be related not only to elevated levels of exercise stress, but also to events in the immediate postexercise period. At this time, peripheral arteriolar dilatation induced by exercise, and reduced cardiac output resulting from diminished venous return secondary to the abrupt cessation of muscular activity, may combine to produce a reduction in blood pressure and decreased coronary perfusion while the heart rate is still increased. Thus, a pathophysiologic basis for the occurrence of arrhythmias at various points during exercise stress is indicated.

Abolition of arrhythmias by exercise: Although the precipitation of arrhythmias by exercise is widely recognized, abolition during exercise of ectopic cardiac activity present at rest is a less appreciated phenomenon. The ability of exercise to abolish arrhythmias present in the resting state has generally been attributed to two mechanisms, both of which are related to the sinus tachycardia resulting from vagal withdrawal and increased sympathetic stimulation accompanying exercise. Thus, sinus tachycardia may inhibit an ectopic focus before its intrinsic discharge reaches threshold potential, an example of overdrive suppression. In addition, there is evidence[10] that rapid stimulation may result in decreased automaticity of Purkinje tissue and thus sinus tachycardia may inhibit automaticity of an ectopic focus.

Spectrum of Exercise-Induced Alterations of Rhythm and Conduction

Supraventricular arrhythmias: A wide variety of supraventricular arrhythmias may be noted in the process of stress testing. Wandering or ectopic atrial pacemakers and sinus arrhythmias are particularly common after exercise.[5] However, although 3 to 5 beat episodes of paroxysmal atrial and junctional tachyarrhythmias occurred frequently during exertion in 3,000 patients studied by Gooch,[5] sustained bouts lasting more than 15 seconds occurred in only 5 patients. Several investigators[2–5] have noted that atrial fibrillation and flutter are only rarely induced by exertion and, when they do occur, revert spontaneously. Indeed, observation of the response of ventricular rate to various levels of activity has provided an excellent method of assessing adequacy of digitalization in patients with atrial fibrillation.[11] This response could not be predicted from the resting heart rate. Finally, rare episodes of sinoatrial block and sinus arrest have been noted during stress testing, usually after termination of exercise.[5]

Conduction defects: Alterations of cardiac conduction involving both the atrioventricular (A–V) node and bundle branches may occur during the course of exercise testing. A–V conduction is accelerated during exertion under normal circumstances[12] and absence of such shortening has been regarded as an abnormal response indicative of A–V junctional block. In addition, the appearance of frank first degree heart block or its progression to more advanced block has also been noted in association with exercise.[2–5] Conversely, preexisting block of the A–V node has been noted to decrease in this setting, a phenomenon that may be related to enhanced conduction velocity due to increased sympathetic stimulation.

Abnormalities of ventricular conduction consisting of intraventricular conduction defects and bundle branch block involving either the left or right bundle branch were observed in 8 of 733 patients undergoing stress testing.[5] Seven of these eight patients had clinical evidence of heart disease. Sandberg[2] reported on a small group of patients who manifested bundle branch block during exertion and in whom the appearance of the defect with mild effort was associated with clinical evidence of cardiac disease. In both of the latter studies the abnormalities of conduction were usually preceded by evidence of incomplete block in the resting electrocardiogram, and they appeared during exercise and disappeared after termination of the stress.

Ventricular arrhythmias: Ectopic beats and tachyarrhythmias of ventricular origin have been frequently described during exercise testing.[13–16] Thus, ventricular dysrhythmias with exertion were noted in 39 percent of patients by Kosowsky et al.,[16] in 31 to 49 percent by McHenry et al.,[14] in 20 percent by Goldschlager et al.[13] and in 30 percent by Blackburn et al.[15] Ectopic ventricular beats were observed most commonly in the postexercise period in all but one study[15] and frequently occurred late in the recovery period. Thus, two thirds of the arrhythmias in one report[1] occurred within 2 minutes of cessation of exercise and the single death reported in a large group of patients with coronary disease occurred suddenly 4 minutes after completion of the exercise test.[13] Salvos of ventricular tachycardia were preceded by single ectopic beats in the vast majority of cases. Premature ventricular contractions occurred with increased frequency with advancing age[14] and higher levels of effort[14,15] of the patients evaluated.

Diagnostic Significance of Ventricular Arrhythmias Precipitated by Exercise

Considerable interest has been stimulated in the diagnostic and prognostic implications of ventricular dysrhythmias occurring during graded bicycle or treadmill exercise testing. Although the significance of these rhythm disturbances has not been firmly established, certain patterns seem evident on the basis of the information currently available.

Debate continues on the significance of exercise-induced ventricular extrasystoles as indicators of the presence of organic heart disease. Several early investigations[17–20] demonstrated the occurrence of ventricular dysrhythmias in apparently normal persons and failed to find a correlation between ventricular ectopic beats elicited during effort and clinical evidence of cardiac disease. Sandberg[2] found that the subset of patients who demonstrated ventricular arrhythmias after light effort also manifested clinical heart disease, and Gooch and McConnell[1] related bursts of ventricular tachycardia to the presence of cardiac abnormalities. These conclusions were supported by McHenry and associates[14] who, while observing ventricular ectopy in more than one third of apparently normal subjects, noted an even greater frequency of ventricular dysrhythmias in patients with clinically evident or suspected cardiac disease. In the patients manifesting these abnormalities, ventricular ectopic beats were provoked by lighter exertion and at lower heart rates and had a greater tendency to be frequent, multifocal or repetitive. In all these studies the criteria for heart disease were based upon clinical evidence; thus, subclinical cardiac abnormalities may well have been present and undetected in the "normal" group.

Zaret et al.[21] evaluated exercise-induced ventricular irritability in a group of patients undergoing coronary arteriography and found coronary atherosclerosis in 72 percent. Multiple vessel disease was significantly more common than in matched patients without arrhythmias. Goldschlager et al.[13] compared a group of patients with ventricular arrhythmias elicited by exertion with a group of patients without such disturbances who had undergone cardiac catheterization and coronary arteriography. These investigators found significant coronary stenosis in 89 percent of patients with exercise-precipitated ventricu-

lar extrasystoles. In addition, they observed a significantly greater prevalence of double and triple vessel coronary artery disease and abnormal left ventricular motion in this group than in patients with coronary disease without arrhythmias. Provoked arrhythmias occurred more frequently during the recovery period in this study. A striking finding was the disappearance of ectopic beats during exercise stress in a high percentage of patients with significant coronary disease.

Although there is no question that ventricular arrhythmias may occur in the absence of organic heart disease, certain conclusions appear justified from the findings cited: (1) Ventricular arrhythmias provoked by exertion occur significantly more frequently in patients who have cardiac disease than in normal subjects; (2) ventricular ectopic beats that occur with minor increases in heart rate, or demonstrate high frequency, multifocal pattern or repetitive firing are particularly suggestive of cardiac disease; (3) patients with coronary atherosclerosis who have ventricular rhythm disorders induced by stress testing have a greater frequency of multiple vessel disease and abnormalities of wall motion; and (4) the termination of ventricular ectopy during exertion does not indicate the absence of flow-limiting coronary atherosclerosis.

Prognostic Significance of Exercise-Induced Ventricular Arrhythmias

Of major interest is the prognostic significance of exercise-induced ventricular arrhythmias. Premature ventricular contractions manifested in a resting electrocardiogram[22,23] or during activities[24] have been associated with an increased incidence of coronary atherosclerosis, subsequent mortality and sudden death.[15] This risk is especially prominent in patients with known cardiovascular abnormalities.[25] However, the resting electrocardiogram has a substantially lower yield than exercise electrocardiography in the detection of ectopic ventricular rhythms.[16] It would seem reasonable that ectopic ventricular beats evoked during exertion might carry serious prognostic implications and thus be of major importance in the issue of sudden death.[26] Long-term epidemiologic studies will be required to provide a definitive answer to this question. However, exercise-elicited ventricular extrasystoles have already been correlated with the coronary risk factors of hypertension and glucose intolerance as well as with ischemic electrocardiographic abnormalities and enlargement of the cardiac silhouette on roentgenographic study.[3] Indeed, in this study population, sudden death occurred in two patients with exertional ventricular irritability. That such potential disasters may be amenable to therapy is suggested by Bryson et al.,[4] who reported in these patients exertional ventricular tachycardia and fibrillation which prompted coronary arteriography, revealing significant coronary atherosclerosis. Subsequently these arrhythmias were abolished by coronary artery bypass graft surgery.

Usefulness of Holter Monitoring Versus Exercise Stress in the Detection of Arrhythmias

Premature ventricular beats elicited by exertion can be evaluated either by prolonged ambulatory monitoring, a costly and time-consuming procedure, or by graded exercise testing. Kosowsky et al.[16] compared the sensitivity of ambulatory electrocardiographic monitoring and treadmill exercise testing in revealing ectopic ventricular activity in 81 patients with and without coronary artery disease. Of 66 patients with a normal resting electrocardiogram, prolonged monitoring was positive for arrhythmias in 27 percent, whereas exercise was positive in 39 percent. Exercise also revealed serious rhythm abnormalities that would not have been suspected by use of monitoring alone. These authors therefore concluded that stress testing was superior to portable electrocardiographic monitoring in the detection of ventricular irritability. In this regard, Blackburn et al.[15] demonstrated a 35 percent increase in the yield of premature ventricular complexes and of multiform and repetitive ventricular ectopic beats during maximal as opposed to submaximal exercise testing. Obviously, these additional arrhythmias would be detected by portable monitoring only if the patient performed activities requiring maximal exertion.

We have been impressed with the capacity of both exercise stress testing and prolonged portable electrocardiographic monitoring as means of detecting ventricular ectopic rhythms. Of 22 patients with angiographically documented coronary artery disease, 5 (23 percent) manifested ventricular ectopic beats on the resting electrocardiogram. Ventricular premature beats developed in 59 percent during exercise and were detected in 82 percent of the group by 10 to 12 hour portable monitoring during normal activity.[27]

Effects of Physical Conditioning on the Frequency of Premature Ventricular Complexes

The effect of physical conditioning on ectopic ventricular beats has not been definitely established. Blackburn et al.[15] evaluated the response of ectopic ventricular beats to physical conditioning in 196 middle-aged, "high risk" men free of clinically manifest heart disease. These previously sedentary subjects were evaluated before and 18 months after a program of progressive exercise conditioning. Among subjects adhering well to the program there was inconclusive but suggestive evidence that the work threshold for ventricular ectopic activity was increased. This finding certainly merits further investigation.

Ventricular Irritability and Termination of Exercise Testing

In light of these data, certain practices have evolved in our laboratory concerning ventricular irritability and the performance of exercise stress testing. Thus, the presence of ectopic ventricular beats in a patient whose condition is otherwise stable immediately before study is not considered a contraindica-

tion to exercise testing. Exercise is begun slowly at low work loads and is terminated on occurrence of significant increase in frequency of ectopic beats or dangerous ventricular arrhythmias such as frequent multifocal extrasystoles, R on T phenomenon, coupled ventricular beats or runs of ventricular tachycardia. In our experience exercise testing has infrequently required interruption because of ventricular arrhythmias. Upon completion of exercise the patient is seated with legs elevated to increase venous return, and the electrocardiogram is carefully monitored for at least 6 minutes.

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Indirect Assessment of Myocardial Oxygen Consumption in the Evaluation of Mechanisms and Therapy of Angina Pectoris

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Exercise testing, applied in a systematic, standardized manner, is a more reliable means of assessing angina pectoris than clinical evaluation. In utilizing exercise testing to determine functional impairment in angina, it is essential to distinguish between external stress, or the load on the skeletal muscles, and internal or cardiac stress. This distinction is critical to meaningful evaluation of angina since the performance of the heart is of primary concern in this syndrome. Evaluation of external exercise capacity alone is limited as a measure of cardiac performance since the relationship between external function and cardiac performance may not be direct. A readily applicable approach to determination of cardiac functional capacity in angina is afforded by indirect assessment of myocardial oxygen consumption ($M\dot{V}O_2$). This is achieved through derived indexes of heart rate and blood pressure, two major determinants of $M\dot{V}O_2$, usually in the form of the product of heart rate × systolic blood pressure × systolic ejection period (triple product) or the product of the first two variables (double product). Although these indexes do not encompass all the major determinants of $M\dot{V}O_2$, they demonstrate a constancy at the point of angina in each individual that is consistent with the occurrence of this syndrome at a peak, critical threshold of $M\dot{V}O_2$ above which regional myocardial perfusion cannot rise. Utilization of indirect indexes of $M\dot{V}O_2$ allows evaluation of the mechanisms of action of a variety of conditions and therapeutic interventions in angina. Thus, enhanced perfusion of ischemic myocardium is suggested by augmentation of the triple product when angina occurs during exercise, as observed after successful aortocoronary bypass graft surgery. Medical therapy of angina acts through a fundamentally different mechanism demonstrated by reduction in the triple product at given levels of exercise with no increase at the point of angina, thus indicating a major effect on the circulatory response to the physical stress. Indirect indexes of $M\dot{V}O_2$ are thus useful in interpreting mechanisms and evaluating therapy of angina but they must be applied with appropriate caution because of their inherent limitations.

Appreciation of the pathophysiology of angina pectoris has provided a rational approach to the diagnosis and treatment of this disorder. The systematic application of exercise in evaluation of angina has played a significant role in advancing physiologic understanding of the syndrome. Exercise has been utilized not only in diagnosis but also as an objective means of assessing clinical severity and investigating the circulatory dynamics associated with angina. Relation of the latter alterations to cardiac energetics in terms of myocardial oxygen consumption ($M\dot{V}O_2$) has been of major importance in elucidating the mechanisms of angina, quantifying functional impairment and clarifying modes of therapy in this syndrome.

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Value of Exercise Testing in Assessment of Angina

Although the symptom of ischemic cardiac pain is the most overt manifestation of the anginal syndrome, assessment of symptomatology is of limited reliability in estimating severity of the disease because of the subjective nature of the symptom and the variability of provoking factors. Use of exercise testing to determine functional status has significantly extended clinical evaluation of the patient with angina. Measurement of exercise capacity provides a reliable, quantitative index of functional impairment in angina not attainable by clinical appraisal alone. Thus, systematic assessment of exercise capacity under controlled conditions in patients with angina yields reproducible results in terms of duration of exertion required to provoke the pain of myocardial ischemia.[1] However, underlying cardiac functional capacity is of primary concern in relation to severity of the disease in angina. Although exercise ability provides a functional index in patients with angina, it does not necessarily reflect cardiac capacity. In the response of the body to external work, the relation between skeletal muscle performance and the load sustained by the heart is not always direct,[2] thereby rendering this method of limited value as a precise indicator of cardiac performance. These qualifications also pertain to maximal total body oxygen consumption ($\dot{V}O_2$ max), traditionally considered the most reliable extracardiac index of overall cardiovascular functional capacity.[3,4] This quantity, like external exercise capacity, may also vary under certain conditions in its relation to cardiac performance during exertional stress.[5,6]

Extracardiac factors modifying response to exercise: It is now appreciated that many factors can modify the cardiac response to any given physical stress and thereby alter angina-limited exercise ability without changing cardiac functional capacity.[2] Among these are reduced environmental temperature,[2] emotional stress,[7] the postprandial state[2] and the acute effects of cigarette smoking,[8] which can, in themselves, augment myocardial mechanical effort. In addition, of course, conditions such as musculoskeletal or peripheral circulatory diseases that impair the function of organ systems other than the heart may significantly diminish exercise capacity. It is therefore apparent that exercise performance may be determined not only by the work load directly imposed on the skeletal muscles, but also by other ambient variables influencing the myocardium. This is exemplified by the reduction in exercise performance (decreased time to onset of angina) that accompanies reduced environmental temperature. In this setting, in which intrinsic cardiac functional capacity may be unchanged, decreased exercise performance is related to the augmented cardiac work load, indicated by the increased heart rate and blood pressure, associated with reduced temperature.[2] Similarly, the fasting state may be associated with enhanced exercise capacity in relation to onset of angina compared with exercise capacity in the postprandial state. Again, the altered performance is unassociated with change in cardiac function and is a result of the reduced work load on the heart, as determined by the circulatory response to a given physical stress, in the fasting state compared with that in the period after a meal.[2] Appropriate interpretation of the preceding results would be obscured if exercise capacity were assessed only in terms of duration of exercise before onset of angina. Thus, to the extent that extrinsic influences alter exertional capacity when anginal pain is the limiting factor, the value of this measure as a means of assessing cardiac performance is diminished.

Relation of $M\dot{V}O_2$ to Evaluation of Angina

It is apparent that an approach more closely reflecting the performance of the heart is required for meaningful evaluation of cardiac function in angina. It must encompass the distinction between external work, as entailed by the activity of the musculoskeletal system, and internal work, represented by the mechanical performance of the heart. The latter can be assessed in terms of cardiac energy utilization which, by virtue of the obligatory aerobic nature of myocardial metabolism,[9] is directly related to the oxygen consumption of the heart ($M\dot{V}O_2$).[10]

Peak $M\dot{V}O_2$: Angina is the result of an imbalance between myocardial oxygen demand and supply that is typically related to a restricted coronary circulation consequent to coronary atherosclerosis.[11] Coronary circulatory reserve is compromised and, in response to increases in $M\dot{V}O_2$, coronary blood flow, and thereby oxygen delivery, cannot be augmented beyond a limit fixed by the degree of arterial obstruction. The level of $M\dot{V}O_2$ at which the disparity between myocardial oxygen supply and demand occurs represents the internal or cardiac threshold for angina. Thus, peak $M\dot{V}O_2$ at the point of angina (hereafter referred to as peak $M\dot{V}O_2$) is an index of maximal tolerated cardiac stress, which is directly related to cardiac functional capacity in angina and may be independent of external work load as determined by the influence of extrinsic factors on the heart. In the absence of alterations in delivery capacity of the coronary circulation, as may occur with progression of coronary artery disease, $M\dot{V}O_2$ at the point of angina is constant for a given patient. Peak $M\dot{V}O_2$ also provides a relative measure of maximal attainable coronary blood flow since coronary blood flow follows $M\dot{V}O_2$ pari passu, as demonstrated both experimentally[12,13] and in man.[6] This relationship is a result of the exclusively aerobic pattern of cardiac metabolism, requiring near maximal oxygen extraction by the myocardium even under basal conditions, thereby precluding use of this mechanism for increasing oxygen supply. Alterations in $M\dot{V}O_2$ are therefore effected by changes in coronary blood flow.[14]

$M\dot{V}O_2$ at angina vs. $M\dot{V}O_2$ at given external work load: In addition to providing a measure of cardiac performance through peak $M\dot{V}O_2$, the foregoing relationships afford insight into mechanisms of therapeutic interventions and other factors that may

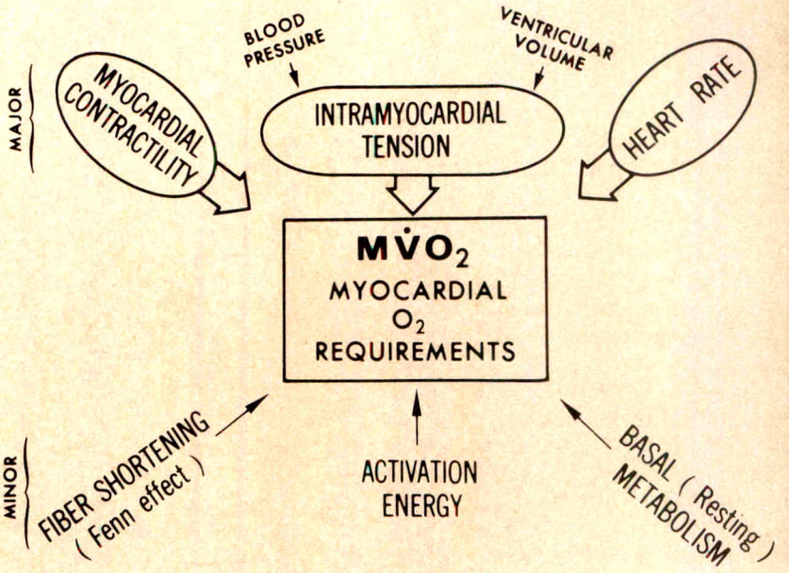

FIGURE 1. The major and minor determinants of myocardial oxygen consumption ($M\dot{V}O_2$).

alter exercise capacity in patients with angina. Therapy in angina is based on restoration of a favorable balance between myocardial oxygen demand and supply, thereby alleviating myocardial ischemia. This balance can be achieved by increasing oxygen supply or reducing demand.[15] An increase in peak tolerated $M\dot{V}O_2$ after an intervention is consistent with increased blood flow and oxygen supply to ischemic areas of myocardium. A decrease in peak $M\dot{V}O_2$ implies diminished myocardial perfusion and increased ischemia, and thus a lower level of maximal tolerated cardiac stress.

Interventions that enhance physical performance in patients with angina by reducing myocardial oxygen requirements are associated with no change in peak tolerated $M\dot{V}O_2$. However, myocardial mechanical effort at any given level of external work is decreased by these interventions and attainment of angina-limiting $M\dot{V}O_2$ is thereby delayed, allowing work of greater intensity and duration. Thus, as emphasized by Goldstein and Epstein,[16] valid interpretation of the mechanism of action of an intervention that alters angina-limited exercise capacity requires knowledge of $M\dot{V}O_2$ both at angina and at a given external work load. Reduction of myocardial oxygen requirements is achieved by attenuating the response to external stress of the hemodynamic variables upon which $M\dot{V}O_2$ is dependent. These include heart rate, intramyocardial tension (directly related to ventricular pressure and volume) myocardial contractility and certain minor factors (Fig. 1).[10] The rationale for this therapeutic approach is consistent with the demonstration of hemodynamic alterations indicative of increased $M\dot{V}O_2$ in association with angina that has been provoked by exercise,[17] catecholamine stimulation[18] or pacing-induced tachycardia[19] or has occurred spontaneously.[20]

Indirect indexes of $M\dot{V}O_2$ (heart rate-blood pressure product): $M\dot{V}O_2$ can be directly determined as the product of myocardial arteriovenous oxygen difference and coronary blood flow, but since both of these measurements require cardiac catheterization, this technique is not feasible for general application. However, indirect approaches to assessment of $M\dot{V}O_2$ have been rewarding as practical means of estimating this quantity. Consistent with their importance as major determinants of myocardial oxygen utilization, derived indexes comprised of blood pressure and heart rate have provided a reasonable approximation of relative $M\dot{V}O_2$. These have included the product of mean aortic pressure and heart rate,[13] the tension-time index[21] (product of the integral of left ventricular pressure during systole and heart rate), the triple product of heart rate, systolic blood pressure and systolic ejection period[7] and the double product of heart rate and systolic blood pressure.[6,22]

These indirect indexes of $M\dot{V}O_2$, although affording ease of assessment, also involve inherent limitations. Thus, they fail to include ventricular volume and the contractile state of the myocardium, two major determinants of $M\dot{V}O_2$. Whereas heart rate and blood pressure are readily determined, measurement of volume and contractility is complex and thus inconsistent with pursuit of a widely applicable approach to $M\dot{V}O_2$. Further, the significance of the duration of ventricular ejection (systolic ejection period) in influencing $M\dot{V}O_2$, and thus the relative advantages of the triple or double product, has been unclear. However, experimental[23] and recent clinical[6,22] studies have suggested that duration of ejection, initially considered a significant determinant of $M\dot{V}O_2$,[21] is relatively unimportant.

Despite these theoretical deficiencies, a close correlation has been demonstrated between $M\dot{V}O_2$ and the heart rate-blood pressure product during exercise in normal young men,[6,22] thus supporting the utility of indirect assessment of $M\dot{V}O_2$. In these studies, performed from the resting state through exercise to 56 percent of maximal capacity, there was a high cor-

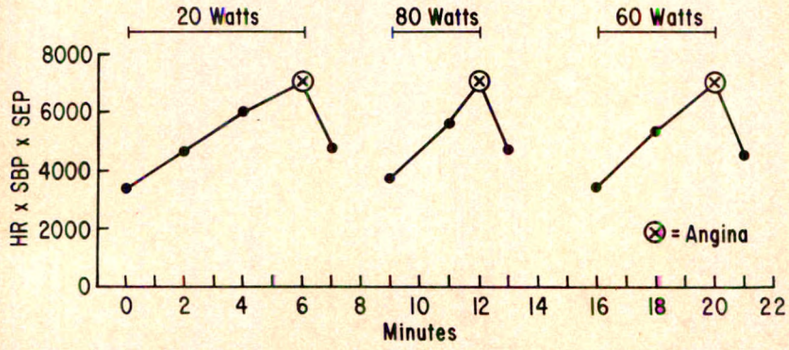

FIGURE 2. Relation of onset of angina to duration and intensity of exercise on the bicycle ergometer and the triple product of heart rate (HR), intraarterial systolic blood pressure (SBP) and systolic ejection period (SEP). Duration of exercise is inversely related to the work load but angina occurs at a constant triple product.

relation ($r = 0.90$) between $M\dot{V}O_2$ and the product of (1) heart rate × peak systolic aortic pressure, (2) heart rate × mean systolic aortic pressure, and (3) heart rate × mean aortic pressure. Heart rate alone also correlated closely with $M\dot{V}O_2$ ($r = 0.88$). The relationship between measured coronary blood flow and the preceding variables was similarly close. However, tension-time index and total body oxygen consumption ($\dot{V}O_2$) correlated less well with $M\dot{V}O_2$. Because these studies were performed in normal young men, appropriate caution is indicated in extrapolating the results to older patients with ischemic heart disease.

Application of Indirect Indexes of $M\dot{V}O_2$ to Angina

Although the importance of heart rate in the precipitation of angina was recognized more than 3 decades ago,[24] this relation was subsequently questioned,[25] and blood pressure was discounted as a significant factor in the production of angina in these early studies.[24,25] These findings may be related to limitations in methodology since they were derived from indirect, cuff blood pressure measurements[24,25] and data obtained after termination of exercise.[24] Recent reevaluation of the relation of heart rate and blood pressure to the occurrence of angina has confirmed the significance of both variables and upheld the applicability of indirect indexes of $M\dot{V}O_2$ to evaluation of angina. Thus, it has been demonstrated that for the individual patient, precipitation of angina occurs at a constant value for the triple product of heart rate, intraarterial systolic pressure and systolic ejection period.[7] This relationship is consistent and independent of variations in the type, intensity and duration of exercise (Fig. 2).[7] Thus, external exertional capacity, as indicated by intensity and duration of exercise, varies as a function of the imposed load. However, provocation of angina is related to attainment of a critical triple product that reflects the stress on the myocardium, the essential factor in the production of angina. These findings provide indirect support for the concept, discussed earlier, that each patient experiences angina at a critical or peak level of $M\dot{V}O_2$, which can be approximated by the triple product and is determined by the delivery capacity of the coronary circulation to the region of lowest threshold for imbalance between myocardial oxygen supply and demand.

Since heart rate-blood pressure indexes of $M\dot{V}O_2$ are constant at the point of angina for a given individual despite their failure to account for several principal determinants of $M\dot{V}O_2$, it is reasonable to conclude that under the conditions of study, the omitted factors either are constant or are so altered that their effects on $M\dot{V}O_2$ are canceled. In such instances, $M\dot{V}O_2$ would, in effect, vary as a function of the readily measurable hemodynamic variables, blood pressure and heart rate, as suggested by the previously cited studies in normal man.[6,22] Whether these findings pertain to ischemic heart disease has not been definitively determined.

Application of rate-pressure product to interpretation of pathophysiology of angina: With use of derived indexes of heart rate and blood pressure to estimate $M\dot{V}O_2$, it is possible to clarify mechanisms of angina occurring under various circumstances. Thus, exercise in the postprandial state is accompanied by an elevated triple product at any given level of external work in comparison to the response in the fasting state, and angina occurs earlier. However, the triple product at the point of angina is the same in the two states.[2] These data suggest that the diminished exercise capacity after a meal is the result of an augmented circulatory response—that is, more rapid increase in heart rate and blood pressure—to exercise associated with this condition and is not related to changes intrinsic to the myocardium and coronary circulation. The unaltered triple product at angina is consistent with the latter conclusion. Likewise, the diminished exertional ability and earlier provocation of angina during exercise after smoking a cigarette is associated with an increased rate-pressure product above that occurring in the control exercise state.[8] An augmented circulatory response to physical exertion at low ambient temperature is similarly productive of angina after less exercise.[2] These studies, which implicate extramyocardial mechanisms in the alteration of exercise capacity under the conditions cited, demonstrate the application of indirect indexes of $M\dot{V}O_2$ to interpretation of pathophysiology in angina.

Evaluation of Therapeutic Mechanisms in Angina by Indirect Assessment of $M\dot{V}O_2$

It has generally been concluded that medical therapy is beneficial in angina pectoris by attenuating the circulatory response to physical or emotional stress.[1-5]

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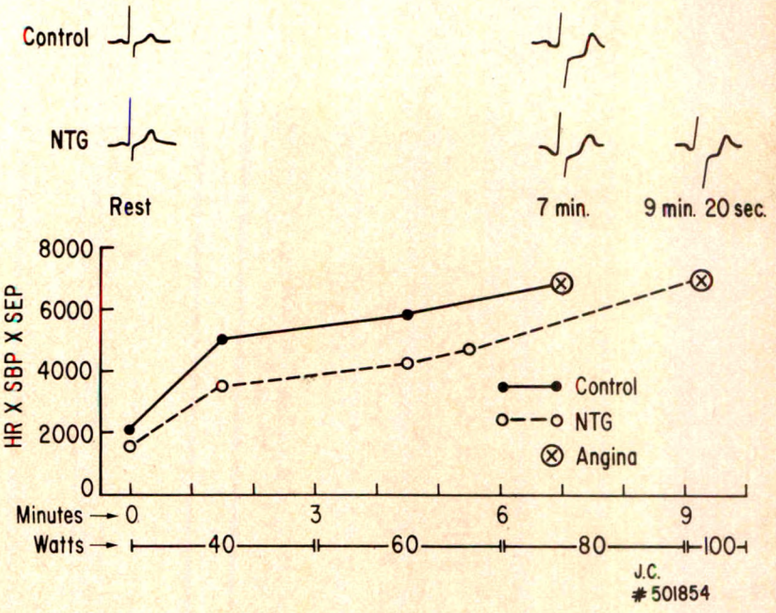

FIGURE 3. Exercise performance on the bicycle ergometer in a patient with coronary heart disease, before and after sublingual administration of nitroglycerin (NTG). The triple product (HR × SBP × SEP) is reduced after administration of nitroglycerin, resulting in increased exercise capacity. However, the triple product at angina is unchanged. Ischemic S–T segment depression (lead V_5) is delayed after administration of nitroglycerin until greater exercise performance has been achieved. Abbreviations as in Figure 2.

Thus, the nitrites and beta adrenergic blocking agents are associated with a reduced rate-pressure product and a delay in attainment of angina threshold. The beneficial effects of the hemodynamic actions of these drugs thus result in enhanced exertional capacity.

Effect of nitrites in angina: The effects of nitroglycerin on exercise performance, the triple product and the exercise electrocardiogram in a patient with ischemic heart disease are demonstrated in Figure 3. After nitroglycerin, ability to perform more exercise is related to a lower triple product at levels of work comparable to those imposed before nitroglycerin. Angina occurs at the same triple product as before administration of the drug but its onset is delayed. These findings, which are consistent with a primary therapeutic action on the hemodynamic determinants of $M\dot{V}O_2$ rather than improvement in myocardial perfusion, have been demonstrated by others for nitroglycerin[26,27] and sublingually administered isosorbide dinitrate.[27] In addition, direct measurement of coronary blood flow at the point of exercise-induced angina before and after nitroglycerin demonstrated no change in peak coronary flow[28] associated with enhanced exercise capacity. This finding is in accord with the results obtained utilizing indirect indexes of $M\dot{V}O_2$.

Although these indirect indexes are useful, their limitations may be appreciated in considering the effects of the nitrites in angina. Thus, the major hemodynamic action of the nitrites in decreasing $M\dot{V}O_2$ is reduction of ventricular volume,[29] the effects of which are not accounted for by the indirect methods. Further, the double product of heart rate and blood pressure is increased at angina after administration of the nitrites, which could be attributable to decreased ventricular volume or increased perfusion of ischemic myocardium. In this regard, it has been suggested that a separate effect of enhanced myocardial perfusion may play a role in the beneficial actions of the nitrites.[15] If such an effect were minor in relation to reduced myocardial oxygen demand, it would not

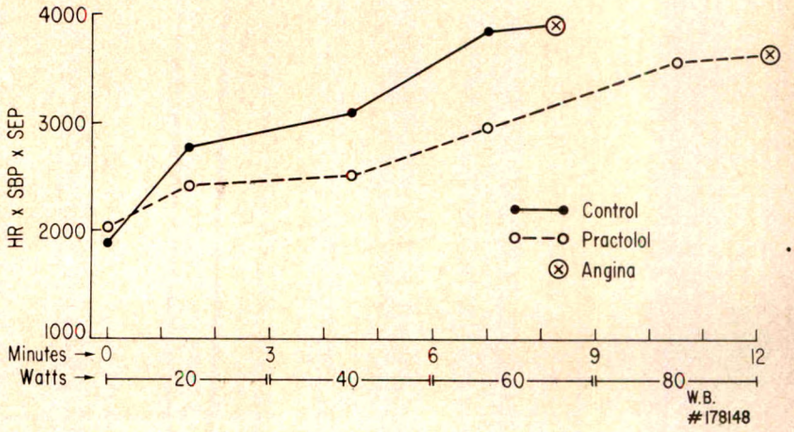

FIGURE 4. Exercise performance (bicycle ergometer) in a patient with coronary heart disease before and after cardioselective beta adrenergic blockade with intravenously administered practolol. The response to exercise of the triple product (HR × SBP × SEP) is attenuated after administration of the drug, resulting in increased duration and intensity of exercise before the onset of angina. Angina occurs at similar triple product before and after administration of the drug. Abbreviations as in Figure 2.

be discernible by indirect assessment of $M\dot{V}O_2$, since the latter methods reflect the resultant of the separate actions of any intervention on $M\dot{V}O_2$.

Effects of beta adrenergic blockade and carotid sinus nerve stimulation in angina: Improvement in effort tolerance by beta adrenergic blockade is consistent with a reduction in $M\dot{V}O_2$ in man during exercise.[15] As shown in Figure 4, the triple product is reduced for a given level of stress and angina is delayed. Although the triple product at angina after beta adrenergic blockade is similar to that of the control study in the example displayed, this finding is uncommon and our data[30] and those of others[31] generally demonstrate a reduction in triple product or rate-pressure product at angina after administration of beta adrenergic blocking drugs. Diminished myocardial oxygen requirement in response to a given level of exercise after propranolol has been confirmed in man by direct measurement of $M\dot{V}O_2$.[23] This may be related to a possible increase in ventricular size due to the depressant effect of these agents on myocardial contractility or to reduction in coronary blood flow. On the other hand, it has been suggested that propranolol may favorably redistribute coronary blood flow[32] and enhance release of oxygen from red blood cells to the myocardium.[33] These latter factors cannot be specifically delineated by indirect methods but the reduction of the rate-pressure product at angina after beta adrenergic blockade suggests that increased myocardial oxygen supply is not a major factor in the beneficial effects of these agents. The salutory effects of carotid sinus nerve stimulation in improving functional status in angina are also the result of reduced $M\dot{V}O_2$, as indicated by increased exercise ability without change in the triple product and reduction of the triple product at submaximal loads of exercise.[34]

Physical training in angina: Physical training, which may augment exertional ability in patients with angina, also appears to act by attenuating the response of the heart to physical stress.[5,35] Thus, the triple product is lower at a given external work load after a training program.[5] The increase in triple product at angina in some trained patients has been interpreted as a possible indication of enhanced myocardial perfusion.[5] However, this could be related to changes in other factors not reflected in the triple product, among them attenuated adrenergic response to exercise stress after a conditioning program,[35] which would reduce $M\dot{V}O_2$ by reducing myocardial contractility while simultaneously allowing attainment of a higher triple product.

Aortocoronary bypass graft: The effects of aortocoronary saphenous vein bypass graft on indirect indexes of $M\dot{V}O_2$ differ from those of other therapeutic modalities previously considered in this discussion and suggest a fundamentally different mechanism of action. Thus, we have evaluated the triple product during exercise in patients with angina before and after coronary bypass graft surgery. Our findings in patients with patent grafts are exemplified in Figure 5. There has been no consistent effect on the triple product during exercise at given work loads before and after operation. However, the triple product at angina before surgery has been exceeded in association with patent bypass grafts and angina has occurred at a markedly greater triple product or exercise capacity has been augmented to the point of volitional fatigue without angina,[36] as depicted in Figure 5.

Similar results have been reported by others comparing the rate-pressure product before and after aortocoronary bypass graft surgery, but utilizing cuff blood pressure.[37] It has been suggested that im-

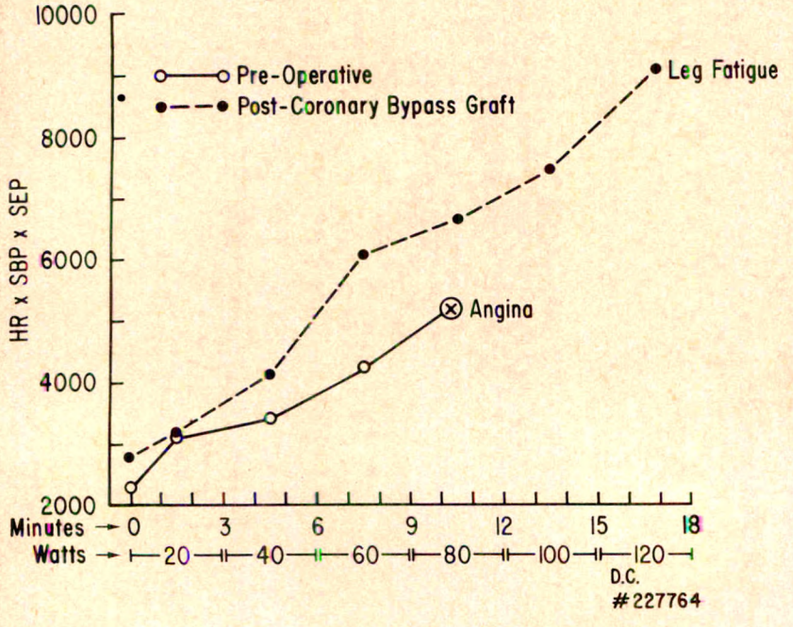

FIGURE 5. Exercise performance (bicycle ergometer) in a patient with coronary heart disease, before and after aortocoronary saphenous vein bypass graft surgery. The bypass graft is associated with increased exercise capacity, abolition of exercise-induced angina and elevated triple product, in contrast to the occurrence of angina with less exercise at a lower triple product before surgery. Abbreviations as in Figure 2.

proved clinical status and exercise capacity following aortocoronary bypass graft surgery may be related not only to graft patency, but also to intraoperative infarction of ischemic myocardium.[16,38] In a study in which this question was evaluated,[37] the great majority of patients with intraoperative infarction did not show clear improvement in exercise capacity as assessed by rate-pressure product and S–T segment changes during exercise although a few manifested enhanced function. The outcome in terms of cardiac capacity in such situations would appear to be the result of the interplay between the functional effects of the graft and the infarction, when the latter occurs.

Indirect indexes of $M\dot{V}O_2$ are of considerable use in the evaluation of angina. Within limits, they allow identification of the roles of external factors and intrinsic myocardial mechanisms in the provocation and therapy of angina. However, because they do not account for several major determinants of $M\dot{V}O_2$, findings based on their use must be interpreted with appropriate caution.

Acknowledgment

The skilled technical assistance of Ms. Martha Wood and Ms. Roberta Brocchini is gratefully acknowledged.

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Experimental Observations on the Effects of Physical Training Upon Intrinsic Cardiac Physiology and Biochemistry

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Hearts of rats conditioned by a moderate swimming program for 8 weeks were compared with hearts of sedentary animals. Hearts of conditioned rats had greater mechanical responses to tachycardia and to increases in preload and afterload, in part because of improved coronary blood flow and oxygen delivery. Energy stores and intermediary metabolism could not account for improved performance of conditioned hearts. Changes in the properties of myocardial contractile proteins with conditioning were characterized by increased adenosine triphosphatase (ATPase) activity and rates of superprecipitation of actomyosin and by alterations in the availability of sulfhydryl groups at the active site of myosin. Hearts of conditioned rats were partially resistant to hypoxia. During hypoxia they converted chemical energy to external work with greater efficiency than hearts of sedentary rats.

The studies indicate that a moderate conditioning program in rats improves potential aerobic cardiac performance. Factors in this improvement include increased capacity for coronary flow and oxygen delivery and higher levels of actomyosin and myosin ATPase activity. Conditioning also confers partial resistance to hypoxia, apparently as a result of improved mechanisms of energy utilization.

Epidemiologic studies suggest that sedentary persons tend to have increased morbidity from cardiovascular diseases. Many investigations have demonstrated the effects of physical training on the integrated function of the cardiovascular system. The trained subject can attain a higher level of exercise and a greater maximal oxygen consumption than the untrained subject. This improved performance is achieved by way of increased cardiac output and peripheral oxygen extraction. The increased maximal cardiac output is associated with a lower heart rate at any level of exercise, but with the same maximal heart rate after physical training as before. Stroke volume is greater at any level of cardiac output in the physically trained state than in the sedentary state. In patients with coronary artery disease, physical training causes heart rate and cardiac output responses similar to those of normal persons. Some early results of training programs in patients who have recovered from myocardial infarction indicate that training may reduce the likelihood of reinfarction or sudden cardiac death.

Although the studies in intact man and animals are informative on the general effects of physical training, studies that elucidate some of the effects on physical training on the heart itself have only recently been conducted. The investigations described here were performed to determine whether physical training in rats affects intrinsic cardiac function, metabolism or biochemistry.

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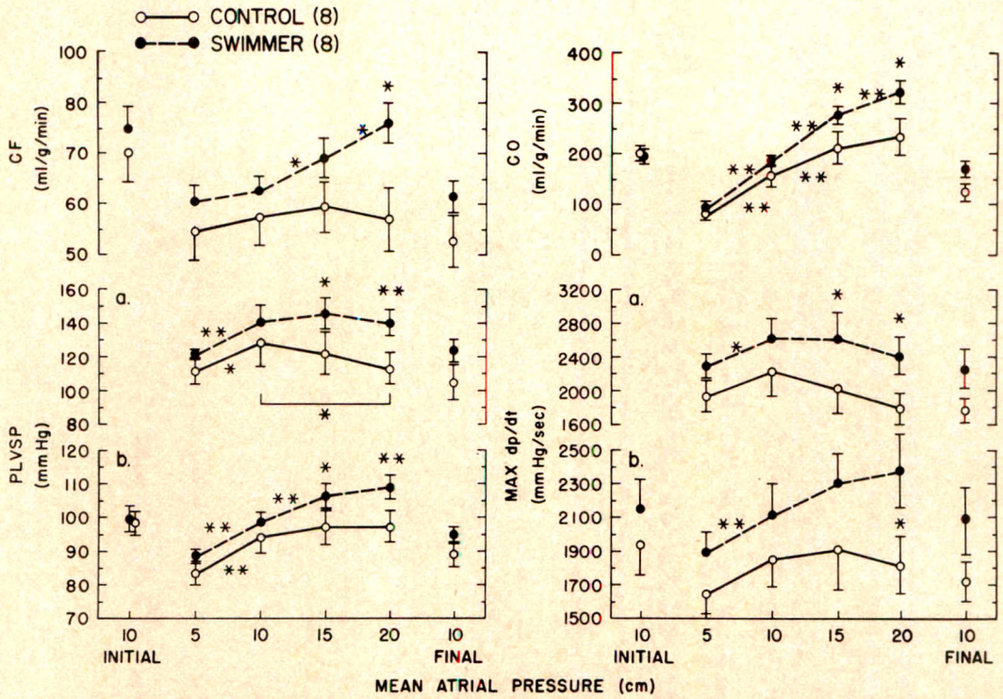

FIGURE 1. Effect of changing atrial pressure on dynamic performance of hearts from conditioned rats (swimmers) and control animals. **a** indicates values obtained when the aortic tubing was clamped. **b** indicates values with an aortic pressure of 85 cm of fluid. **Asterisks along the lines** indicate that mean points among swimmers or controls are significantly different. **Asterisks above the points** indicate that at that atrial pressure the difference between swimmers and controls is significant. * = $P<0.05$; ** = $P<00.1$. CF = coronary blood flow; CO = cardiac output; Max dp/dt = maximal rate of pressure rise; PLVSP = peak left ventricular systolic pressure. (Reproduced by permission from Penpargkul and Scheuer.[2])

The Training Program

Male rats weighing 200 to 240 g were made to swim 75 minutes twice a day, 5 days a week, usually for 8 weeks. Matched sedentary control rats from the same shipment as the swimming animals were kept at normal cage activity for the same periods. Except for the swimming protocol the two groups were treated identically. The details of this protocol have been published previously.[1]

Perfused Heart Studies

To study the intrinsic mechanical function of these hearts as a pump and as a muscle, hearts were perfused in an isolated working rat heart apparatus with a bicarbonate buffer containing 5 millimolar of glucose.[2] The apparatus permits evaluation of cardiac function in the presence of a fixed aortic pressure and a controlled left atrial pressure, with the heart rate regulated by pacing and measurements made of coronary flow, cardiac output, left ventricular pressure and maximal rate of pressure rise (dP/dt), myocardial oxygen consumption and lactate and pyruvate production.

Cardiac function under steady state conditions: In the first series of experiments, hearts were perfused under steady state conditions for periods of 1 hour. Although the trained intact rats had bradycardia, when the hearts were perfused in the isolated perfusion apparatus without control of heart rate, the rates of hearts from sedentary animals and from conditioned animals were virtually identical. Under these steady state conditions, hearts from trained rats had greater cardiac output and external cardiac work than hearts of sedentary animals. Of more significance, the hearts of conditioned rats responded to a 15 percent increase in heart rate by an increase in cardiac work, whereas hearts of sedentary animals did not respond to tachycardia. With the increment in heart rate, myocardial oxygen consumption increased only in hearts of trained rats, whereas the production of lactate and pyruvate, products of glycolytic metabolism, increased with tachycardia only in hearts of sedentary animals.

Effect of increasing left atrial pressure: Figure 1 demonstrates the effects of increasing left atrial pressure on hearts of sedentary and conditioned animals in the working rat heart apparatus. The increase was associated with increased coronary flow only in hearts of conditioned animals. Cardiac output increased in both groups, but was significantly greater in hearts of conditioned rats than in hearts of sedentary control animals. Peak left ventricular systolic pressure and maximal dP/dt also increased to a greater extent in hearts of conditioned animals. When the heart was made to contract isovolumically by clamping the aortic tubing, the left ventricular pressure and dP/dt levels were higher in hearts of conditioned rats. Therefore, in terms of cardiac output, pressure and dP/dt, hearts of conditioned ani-

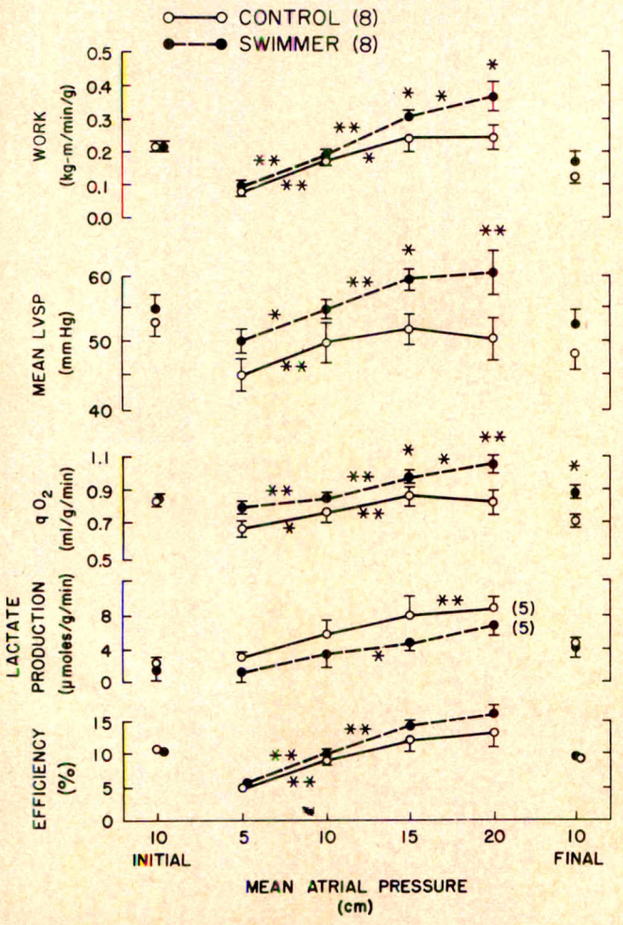

FIGURE 2. Effect of changing atrial pressure upon work, mean left ventricular systolic pressure (LVSP), oxygen consumption (qO_2), lactate production and efficiency. Designations as in Figure 1. Work and metabolic values are per gram dry weight. (Reproduced by permission from Penpargkul and Scheuer.[2])

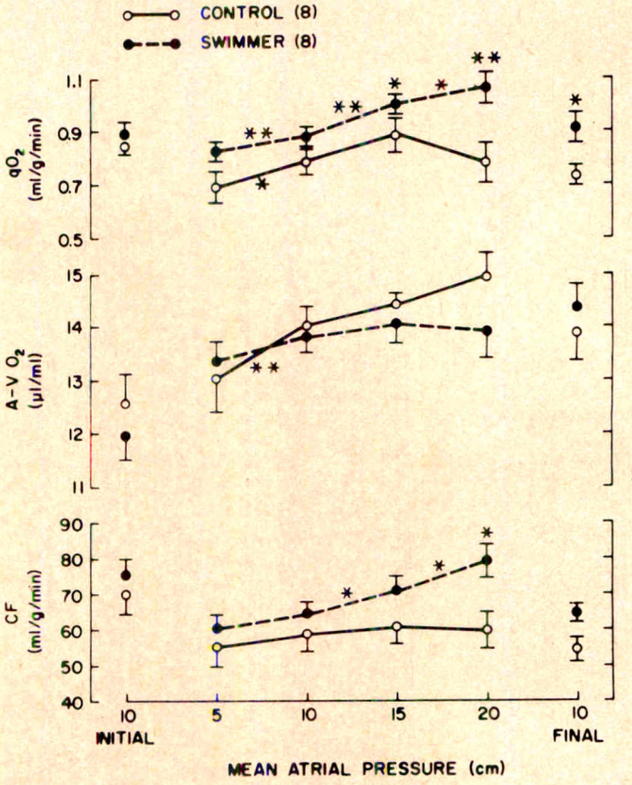

FIGURE 3. Mechanisms of oxygen delivery to the myocardium with increasing atrial pressure. A–V O_2 = extraction of oxygen across the myocardium; CF = coronary flow per gram dry weight; qO_2 = myocardial oxygen consumption per gram dry weight. Symbols as in Figure 1.

mals had a greater cardiac reserve capacity to respond to the stress of increasing preload or afterload. Since hearts were contracting from the same end-diastolic pressure, the greater pressure and dP/dt achieved during isovolumic beats implies increased contractility in hearts of conditioned rats.

Figure 2 shows the results of the same experiments in terms of calculated work, mean left ventricular systolic pressure and metabolic measurements. With increasing atrial pressure, external work and mean pressure were greater in hearts of conditioned rats, as was myocardial oxygen consumption. Lactate production, the product of nonoxidative metabolism, tended to be greater in hearts of sedentary animals. Although cardiac efficiency increased with increasing atrial pressure in both groups, there was no significant difference between hearts of sedentary and conditioned rats.

Mechanism of oxygen delivery: Figure 3 shows the mechanism of oxygen delivery in these experiments.[3] Although oxygen consumption increased significantly with increasing atrial pressure in both groups, the increase was greater in hearts of conditioned rats. This increase in the conditioned animals was achieved by the increase in coronary flow and no change in the extraction of oxygen across the myocardium. In hearts of control animals, the increased oxygen delivery was achieved by a greater oxygen extraction and was not associated with an increase in coronary flow. This finding of increased oxygen extraction in hearts of sedentary rats without augmented coronary flow implies a limitation in coronary flow reserve in these animals and is consistent with previous observations[4–6] of increased myocardial vascularity induced in rats by physical training.

The ratio of oxidative to glycolytic adenosine triphosphate (ATP) formation was higher at all levels of cardiac work in the hearts of conditioned rats.[2]

Implications of studies: These studies in isolated perfused working rat hearts demonstrated that hearts from conditioned rats have a greater intrinsic cardiac reserve capacity to respond to tachycardia, increasing preload and increasing afterload in terms of cardiac output, pressure development and maximal rate of pressure development. The results imply improved potential function of the heart both as a pump and as a muscle. The mechanism of increased reserve appears to be in part a greater capacity for in-

creasing coronary flow and oxygen delivery in hearts of conditioned rats.

Studies on Energy-Related Metabolism

Energy Stores and Energy Release

To determine if some other cause for increased energy availability could be found, hearts from conditioned and sedentary animals were analyzed for glycogen, lipids and high energy phosphates.

Cardiac glycogen: Figure 4 shows the effects of physical training on endogenous cardiac glycogen stores. Cardiac glycogen serves as an endogenous substrate store and reservoir for emergency energy formation. Hearts of conditioned rats had greater endogenous glycogen stores than hearts of sedentary animals. Figure 4 also demonstrates that this glycogen could be mobilized for exercise during a short swim or with the beta adrenergic stimulus of parenterally administered isoproterenol. This modest increase in cardiac glycogen availability would not deliver a great deal of energy but could be important in borderline hypoxic states.

Lipids and high energy phosphates: Endogenous triglycerides are also a potential reservoir for energy formation, and these lipids were slightly decreased in the hearts of conditioned animals.[1,7] Studies of the metabolic conversion of glucose to lactate or carbon dioxide showed no difference between hearts of sedentary and conditioned animals during aerobic conditions, but during hypoxia there was a tendency for greater conversion to lactate in hearts of conditioned animals.[3] Studies of free fatty acid metabolism by conditioned hearts also showed a slight increase in turnover of fatty acid through the triglyceride pool.[3,7] The levels of high energy phosphate stores, creatine phosphate and adenosine triphosphate, were similar in hearts of sedentary and conditioned animals.[1]

Therefore, in terms of metabolism of fatty acids and glucose, the main sources of cardiac energy, and of high energy phosphate stores, there appeared to be no major difference in hearts of physically trained animals and of sedentary animals that could account for the difference in cardiac performance.

Pyruvate kinase and cytochrome oxidase: The question remained whether there were alterations in the pathways of energy liberation. To investigate this possibility, the activity levels of pyruvate kinase, a marker for the glycolytic pathway, and cytochrome oxidase, a marker for the oxidative pathway, were measured in hearts of sedentary and conditioned rats.[8] Cytochrome oxidase levels were not different in the two groups of hearts, whereas pyruvate kinase values were 50 percent higher in hearts of conditioned than in sedentary animals. This finding confirmed the work of Oscai et al.,[9] who demonstrated no increase in oxidative enzymes in hearts of trained animals. Therefore, we concluded that the beneficial effects of physical training probably cannot be attributed to an increase in the capacity of the myocardial cell for aerobic energy formation.

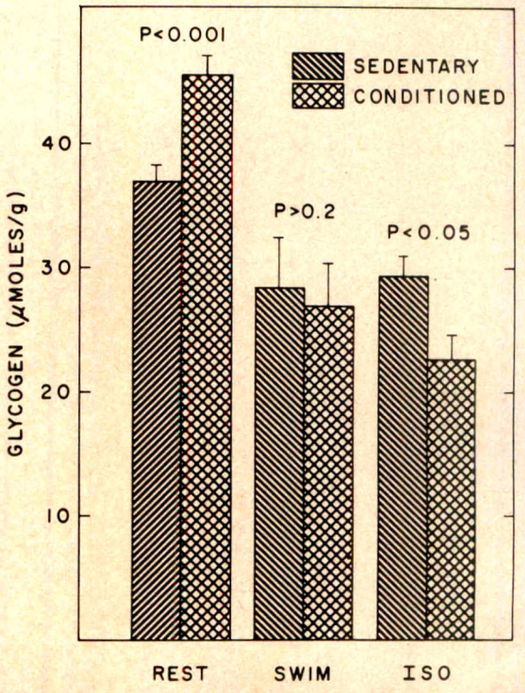

FIGURE 4. Effects of swimming upon myocardial glycogen levels. Values for rest were taken 36 hours after the last swim (conditioned rats). Values for swimming were taken immediately after a 75 minute swim (sedentary and conditioned rats). Values for isoproterenol (ISO) were taken 30 minutes after subcutaneous injection of 50 μg/kg in both groups.

Energy Utilization

Since the studies of the energy production pathways provided evidence for only modest potential increases in energy delivery it became important to investigate some of the mechanisms of energy utilization. For these studies animals swam 90 minutes a day, 5 days a week for periods of 4, 6 and 8 weeks; an additional group swam 75 minutes twice daily for 8 weeks.

Calcium and magnesium ATPase: Figure 5 demonstrates the effects of these swimming programs on the enzymatic capacity to split ATP by actomyosin (ATPase) extracted from hearts of conditioned and sedentary animals.[10] Calcium ATPase studied in the presence of high ionic strength solutions showed increased activity after 6 and 8 weeks of the swimming program. The magnitude of increase was linearly related to the total number of hours that the animals swam. Magnesium ATPase, studied at lower ionic strengths, also increased with the swimming program.

Superprecipitation of actomyosin: Another measurement of actomyosin activity is the rate at which an actomyosin gel superprecipitates in the presence of ATP. Figure 6 shows that the rate of superprecipitation of actomyosin gels was significantly higher in preparations from hearts of conditioned animals than in those from hearts of sedentary animals. The increased actomyosin ATPase activity and the

faster rate of superprecipitation correlate well with the suggested increased contractility of the hearts from conditioned rats as demonstrated in the isolated working perfused heart apparatus.

In these studies of actomyosin the heart weights were the same in control and trained animals except in the group that swam 8 weeks for 150 minutes daily. The conditioned rats in this group had cardiac hypertrophy.[10] Thus, these studies demonstrate an increase in ATPase activity that occurs before the onset of hypertrophy but continues into the hypertrophic phase. This finding is in contrast with the re-

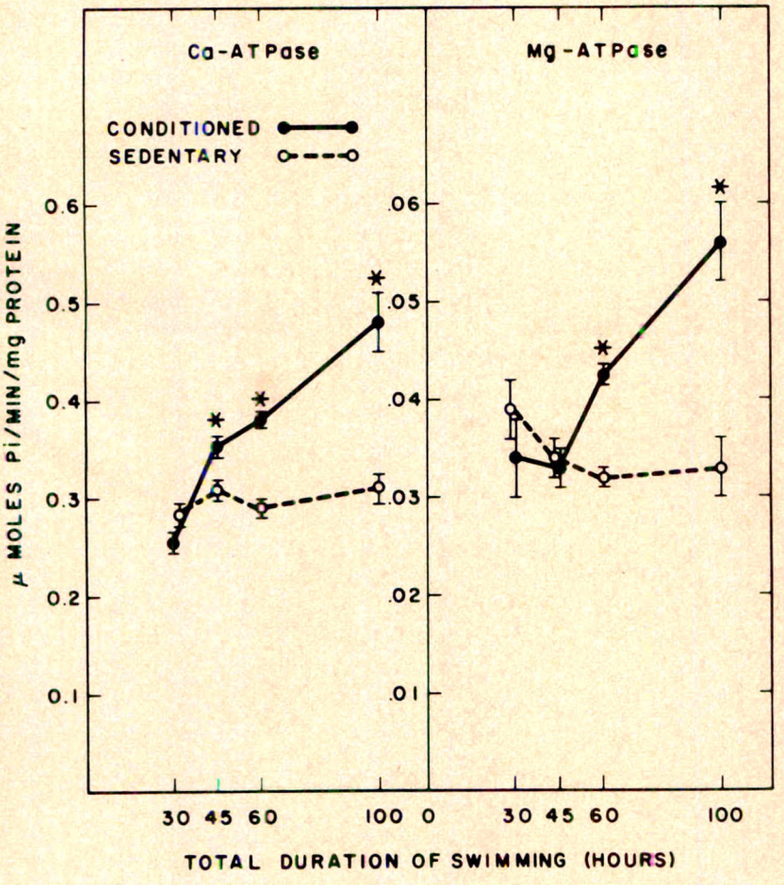

FIGURE 5. Effect of total duration of swimming on calcium (Ca^{++})- and magnesium (Mg^{++})-stimulated ATPase activities of cardiac actomyosin. Data are means ± standard error. **Asterisk** indicates $P < 0.01$ when comparing hearts from control and conditioned animals. 30, 45 and 60 hours represent swimming 90 min/day for 4, 6 and 8 weeks, respectively; 100 hours represents swimming 150 min/day for 8 weeks. Swimming was conducted 5 days/week. (Reproduced by permission from Bhan and Scheuer.[10])

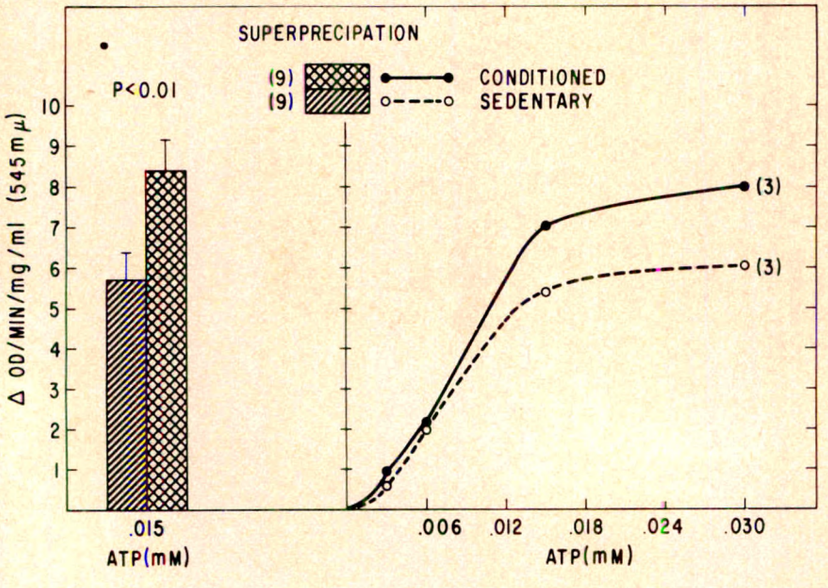

FIGURE 6. Rate of superprecipitation of actomyosin from hearts of conditioned rats. **Curves on right** show rate of superprecipitation (ΔOD/mg per ml per min) as a function of adenosine triphosphate (ATP) concentration. **Bars on left** show mean rates of superprecipitation for nine hearts at 0.0015 millimoles ATP. (Reproduced by permission from Bhan and Scheuer.[10])

duced ATPase activity that accompanies decreased contractility when hearts are made hypertrophic with hemodynamic overload.[11]

Pure myosin ATPase activity: To validate the enzymatic changes in the contractile proteins, pure myosin was isolated from hearts of conditioned rats, and the ATPase activity was studied.[12] Physical training was associated with a 30 percent increase in pure myosin ATPase activity. To elucidate the mechanism of this increased activity, the myosin was reacted with a number of agents that changed the confirmation of the active site of the enzyme. It was demonstrated that ethylene glycol, which disrupts some of the bonds at the active site, had a more powerful effect on myosin from control than from conditioned hearts. Iodoacetamide and 5,5′-dithiobis-(2-nitrobenzoic acid), both agents that bind sulfhydryl groups at the active site, also had a greater effect on myosin from control hearts than from conditioned hearts. These results are consistent with the interpretation that a conformational change at the active site of myosin is induced by physical training in hearts of conditioned rats and is responsible for an alteration in the enzymatic activity. This change appears to be closely related to the availability of sulfhydryl groups at the active site. Therefore, these studies on the energy utilization phase of cardiac metabolism demonstrate a change in the enzymatic activity of the proteins that might be partially responsible for increased cardiac reserve in the hearts of animals that have been conditioned.

Effects of Hypoxia on Function and Metabolism of Conditioned Hearts

Since epidemiologic evidence suggests that one effect of physical training may be to increase the resistance of the heart to myocardial ischemia, but not to prevent the development of atherosclerosis, we[13] conducted further experiments in the isolated heart apparatus to investigate how hearts from conditioned rats respond to hypoxia. The first studies were performed in an apparatus in which the heart beats isovolumically. These demonstrated that hearts of conditioned rats tended to have a smaller increase in end-diastolic pressure than hearts of sedentary rats during hypoxia but that developed left ventricular systolic pressure and maximal dP/dt were not improved by physical training. There were no differences in values for oxygen delivery, lactate production, lactate/pyruvate ratio and accumulation of the reduced form of nicotinamide adenine dinucleotide (NADH), as measured by epicardial fluorimetry during hypoxia in hearts of sedentary and conditioned rats.

Hypoxia and cardiac performance: Figure 7 shows the effect of hypoxia on hearts in the isolated working rat heart apparatus. Here the hearts were perfused first under aerobic conditions at 10 cm atrial pressure and then underwent hypoxic conditions while the atrial pressure remained at 10 cm and was then raised to 20 cm. A recovery period followed during which perfusion conditions were the same as in

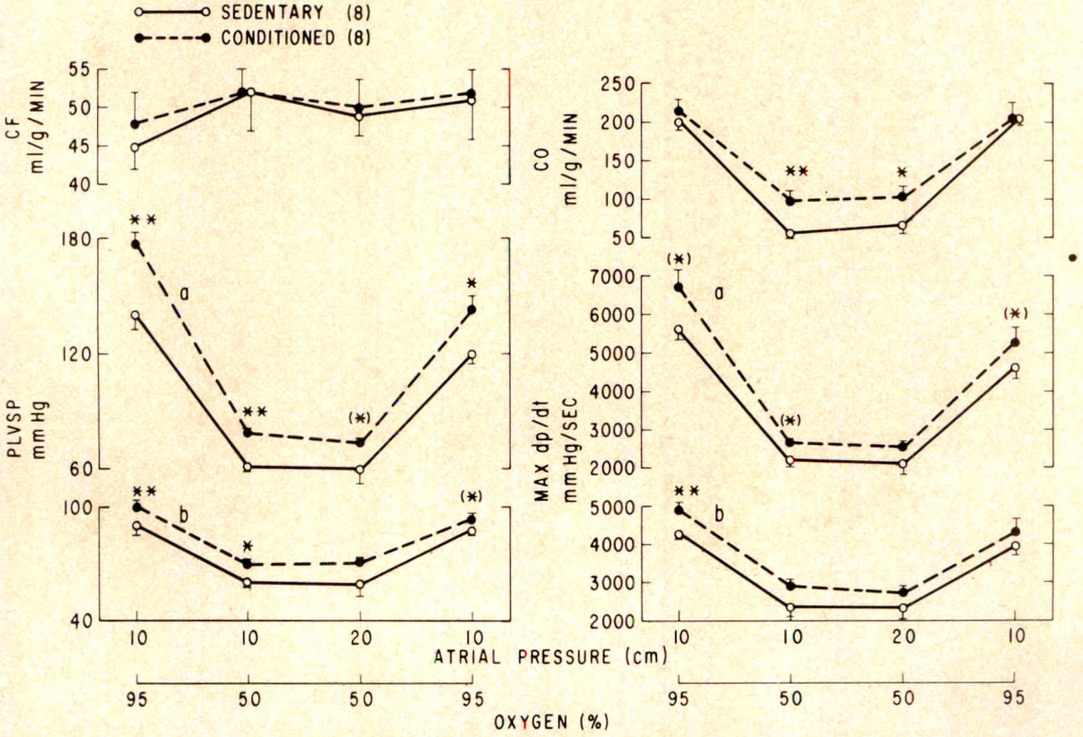

FIGURE 7. Effects of hypoxia on the performance of conditioned hearts in the working rat heart apparatus. Symbols as in Figure 1. (Reproduced from Scheuer and Stezoski[13] by permission of the American Heart Association, Inc.)

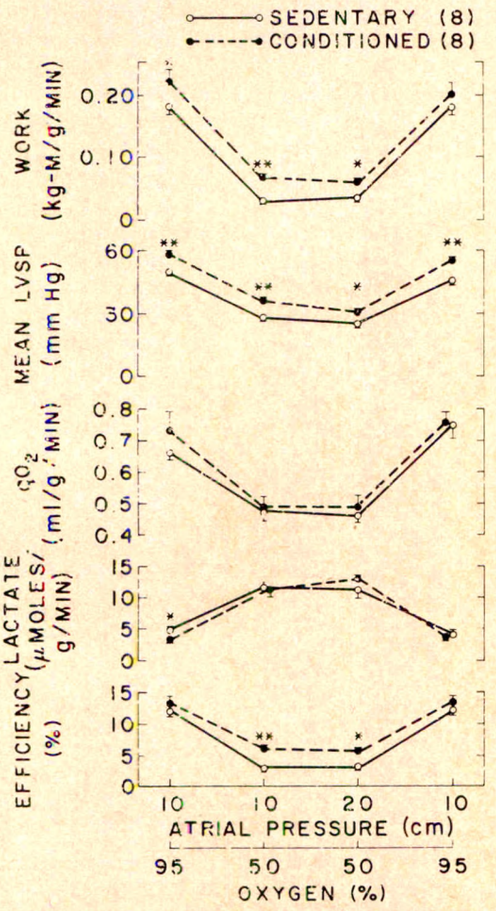

FIGURE 8. Cardiac work and metabolism in conditioned hearts during hypoxia in the working rat heart apparatus. Designations as in Figure 2. Work, qO_2 and lactate output are per gram dry weight. (Reproduced from Scheuer and Stezoski[13] by permission of the American Heart Association, Inc.)

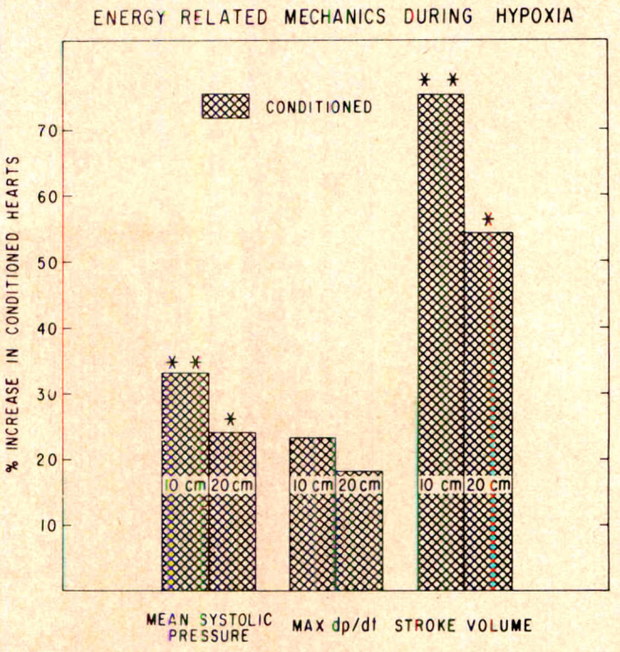

FIGURE 9. Percent increase for conditioned hearts over sedentary hearts in energy-related functions. **Asterisks** indicate statistical significance as in previous figures. Max dp/dt = maximal rate of pressure rise.

the control period. During hypoxia, cardiac output was almost twice as high in hearts of conditioned rats as in those of sedentary control rats. There was a slightly greater left ventricular pressure development but no significant difference during hypoxia in maximal dP/dt. Also the pressure and dP/dt failed to respond to an increase in preload or afterload, indicating that the heart had lost its reserve capacity to respond to stress.

Cardiac work and metabolism during hypoxia: Figure 8 shows the external work and pressure relations in these hearts together with the metabolic findings. External cardiac work was almost twice as great during hypoxia in hearts of conditioned rats as in those of sedentary rats, and mean left ventricular systolic pressure, which relates to wall tension, was only slightly greater during hypoxia in the conditioned rats. There was no difference during hypoxia between the two groups in myocardial oxygen consumption or lactate production values, thus suggesting that energy delivery during hypoxia was the same in hearts of sedentary and conditioned animals. External efficiency was twice as great during hypoxia in hearts of conditioned animals as in hearts of sedentary animals. Thus, hearts of conditioned animals had greater cardiac output, cardiac work and mean pressure performance than hearts of sedentary animals during hypoxia without any evidence of an increase in energy production. High energy phosphate stores and glycogen levels were the same during hypoxia in hearts of conditioned and sedentary rats.[13]

Figure 9 shows the percent increase of performance of hearts of conditioned animals over the control level during hypoxia. There was a 20 to 30 percent greater mean systolic pressure in hearts of conditioned rats during hypoxia but a 55 to 70 percent greater stroke volume. There was no significant difference in maximal dP/dt. When the end-diastolic pressure is the same, as it was in these experiments, mean systolic pressure relates most closely to wall tension, maximal dP/dt correlates with contractility and stroke volume correlates with extent of fiber shortening. These three factors are primary determinants of energy utilization in the myocardium per heartbeat. Tension and contractility are the major determinants of energy consumption, whereas fiber shortening against a load costs very little energy. Therefore, by increasing the stroke volume, and thus its fiber shortening, the conditioned heart would increase its cardiac work efficiently with little change in energy utilization.

Comments

Aerobic performance of hearts of conditioned rats in the working rat heart apparatus was improved as

measured by the responses to rapid pacing and to increased preload or afterload. This improvement was related in part to a greater capacity for increased coronary flow and oxygen delivery to the myocardium.

Hearts from conditioned rats had a slight increase in endogenous glycogen stores, which could be mobilized by stressful stimuli. Triglyceride levels were slightly depressed in hearts of conditioned animals, and levels of high energy phosphate compounds were normal. When studied in the arrested state, conditioned hearts appeared to have a faster turnover of the triglyceride fatty acid pool but no other differences in basal glucose or fatty acid metabolism.

Oxidative enzymes were not increased in hearts of conditioned rats, but actomyosin and myosin ATPase activity levels in these hearts were increased in proportion to the severity and duration of the conditioning process. This increase in ATPase activity was associated with a higher rate of actomyosin superprecipitation.

When studied in the working rat heart apparatus, the performance of hearts of conditioned rats appeared to be relatively resistant to hypoxia. This appeared to be due not to an improvement in energy formation but to more efficient mechanisms of energy utilization.

Many questions remain unanswered by these investigations. In most of the studies hypertrophy of the heart was absent. Therefore, the information may not be relevant to the subject who undergoes an extreme training program and manifests cardiac hypertrophy. It is possible that some training programs may be beneficial and others deleterious to the heart. We do not know the optimal program for promoting cardiac benefits or how the effects of training can be maintained once they have been developed. Finally, the experiments described were performed in young to middle-aged rats with a normal heart. Extrapolation of these in vitro results to intact human subjects who may have cardiac disease must be made with caution.

Acknowledgment

We are grateful for the technical assistance of Mr. S. William Stezoski and Ms. Patricia Pisanelli, and for the expert secretarial assistance of Ms. Carol Gundlach and Ms. Donna Costabile.

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Medical Screening of Patients with Coronary Artery Disease

Criteria for Entrance into Exercise Conditioning Programs

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Although considerable emphasis has been placed on stress testing and physical training of patients with coronary artery disease, data on safe and thorough preliminary medical evaluation are scarce. Because the routine history and physical examination are not sufficient to protect the exercising subject, medical screening attempts a thorough analysis of the patient's motivation, physical status, possible risk factors and the probability of benefit.

Motivation is a critical factor since training for prolonged periods of time at high levels of heart rate and oxygen consumption may be required. Patients who have unstable angina or who may be harmed by increased myocardial oxygen requirements must be excluded. Concomitant influencing diseases and certain medications may also be causes for rejecting a patient. Valvular heart disease and severe systemic hypertension are not associated with benefit from exercise conditioning. The screening physician must exclude patients with certain abnormal electrocardiographic patterns, such as bilateral bundle branch block and type II second degree atrioventricular block, and he must be assured that he is dealing with coronary artery disease, not a pathologic process that mimics it. When these principles are applied, few persons in organized programs of exercise conditioning should suffer, and the yield of good results should be enhanced.

The advent of coronary artery bypass surgery has not eliminated the need for continued medical treatment of patients with coronary artery disease. During the last decade, interest in exercise conditioning programs for such patients has increased because of clinical and experimental evidence of benefit.[1,2] Carefully designed training protocols[3] have been developed to observe, train and record results in such patients. Unfortunately, the majority of exercise programs are unsupervised and frequently undertaken by the patient on his own. As yet, unsupervised training has not resulted in significant mortality. However, the increasing awareness of exercise benefits both to the patient with coronary artery disease and to persons at risk of such disease suggests that the exercise fad itself may eventually become a risk factor.

The nonuniformity of training programs is paralleled by a similar inconsistency in preexercise medical screening. A "good history and physical examination" are not in themselves sufficient to protect the exercising subject.[4] Although these procedures are prerequisites to prevention of complications, they represent a somewhat crude assessment of participant risk. Yet, when they are combined with more subtle assessments, such as exercise stress testing, it is possible to eliminate most unsuitable subjects.

A review of published reports reveals few data on preliminary medical evaluation for stress testing and training. This paper therefore presents guidelines for patient safety and rejection, emphasizing key

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aspects of the evaluation and the differences between a routine examination and a medical screening.

Who Should Be Screened?

All patients with known or suspected coronary artery disease deserve careful screening. In addition, all adults of 40 years or over contemplating exercise training should be evaluated, as should persons of any age with potentially complicating illnesses, coronary risk factors or a possible past history of heart disease.

Screening Aims

The screening analysis has three major aims: (1) assessment of motivation, (2) elimination of undue risk, and (3) evaluation of potential benefit. These factors can be investigated by a specific history and physical examination in association with some laboratory procedures.

Motivation

Motivation, often neglected in preexercise evaluation, is a major factor in program adherence and patient safety. Cardiovascular conditioning may be necessary for months to years at levels of activity requiring a high heart rate and oxygen consumption at 65 to 85 percent of the maximal rate. Thus, poorly motivated subjects are frequently training failures. Overly motivated or overly competitive subjects may be dangerous to themselves or to the program. Such persons tend to follow rules and protocol poorly and may challenge the most fit members of the group or exceed their musculoskeletal and cardiorespiratory capacities.[7] The dropout rate of poorly or overly motivated subjects may be high. Motivation is assessed principally thorough a carefully taken history that stresses the patient's personal and social habits.[8] The five principal factors that influence adherence to an exercise program are listed in Table I.

People agreeing to train expect certain rewards. In general, these are positive feelings of health and well-being and the belief that exercise will favorably affect survival and functional capacity. Such feelings encourage program participants to continue even though training may be difficult and time-consuming. In addition, people who are likely to adhere to a program typically enjoy exercise. In many cases they have previously participated in exercise programs or sports and the return to training represents a combination of therapy and relaxation. Lastly, well motivated subjects, although questioning may indicate that they have a competitive personality, have control of their aggressive drives, have a positive attitude toward exercise and are not bored by exercise, realizing that it is therapy, not merely an enforced, meaningless obligation.

The screening physician must also obtain other information that may affect adherence to the program.[9] Does the subject understand the program? Does his working or professional schedule allow it? Can he agree to participation and supervision in a group program in which he will receive data about his performance and his physical safety will be assured? Has he performed well in past programs and adhered realistically to dietary or other measures designed to reduce risk factors? Finally, the reasons for referral of a patient to a training program must be scrutinized. Often a subject is referred only because medical treatment has failed him.

TABLE I

Motivation—Five Factors Influencing Program Adherence

1. Prior history of habitual exercise or participation in sports
2. Competitive personality traits
3. Fear of incapacitation
4. Desire for good health and feeling of well-being
5. Enjoyment of exercise without boredom

TABLE II

Clinical Assessment of Undue Risk

History
1. Increasing angina
2. Duration since myocardial infarction
3. Congestive heart failure or low cardiac output
4. Symptomatic arrhythmias
5. Medication
6. Severe systemic diseases
7. Exertional hypotension or syncope

Physical examination
1. Congestive heart failure
2. Abnormal precordial pulsation or thrill
3. Murmurs consistent with valvular disease
4. Diminished or abnormal arterial pulsations
5. Elevated diastolic blood pressure with retinopathy

Laboratory evaluation
1. Specific abnormal electrocardiographic patterns
2. Chest X-ray abnormalities
3. Abnormal results of blood studies

Undue Risk

The second major aim of screening is to identify and reject patients who could be harmed by an exercise conditioning program. For this purpose, a thorough and total medical evaluation must be made. The assessment must include an incisive review of the patient's history, a careful physical examination and specific laboratory procedures (Table II). Patient safety and program success require that this evaluation, although brief, review both the gross and subtle features of actual or potential disease.

History

From the history, the examiner can determine whether the subject is threatened by inordinate myocardial oxygen requirements, the hemodynamic consequences of medication during training, or other systemic diseases. Patients with coronary artery disease may remain well compensated when metabolic demand and vascular supply are matched. Because

TABLE III

Major Causes for Rejecting Patients

1. Clinically unstable or inadequately treated disease
2. Clinically important complicating illnesses
3. Specific medications
4. Diseases mimicking coronary artery disease
5. Poor motivation

exercise may alter this relation, evidence of inadequate oxygen supply must be sought in the history.

Unstable angina: Although unstable angina is the most common deterrent to training, it is often difficult to identify. Standard questioning may not reveal that the subject who now has pain on moderate effort also has spontaneous ischemic pain, nocturnal pain, an increasing need for nitrites, more prolonged periods of angina or has had to pace himself to a lower level of energy expenditure. This changing anginal pattern may assume many forms. There may be an obvious and severe intensification of ischemic symptoms (crescendo or preinfarction angina), or the signs may be insidious and more slowly progressive. Retrospective analysis of the patterns of pain leading to myocardial infarction frequently shows a slow and gradual intensification of complaints culminating in an acute coronary event. The screening physician must appreciate these subtle changes if he is to ensure that patients with these symptoms do not enter the training program. In patients who are convalescing from a myocardial infarction, myocardial oxygen consumption should not be inordinately augmented until complete healing has occurred. A period of about 3 months is a standard interval for ensuring safety.

Reduced ventricular function and myocardial reserve: Patients with symptomatic congestive heart failure or low cardiac output (weakness on effort, dyspnea, fatigue and malaise) have reduced ventricular function and myocardial reserve. Increasing myocardial oxygen requirements in such patients can only be harmful.[10] The occurrence of symptomatic cardiac arrhythmias increases oxygen demand inappropriately. The arrhythmia must first be identified by type and then treated. All of the aforementioned situations that inappropriately increase myocardial oxygen requirements can be identified by a carefully taken history, then treated and potentially controlled. Upon return to a stable condition, the patient may again be considered for training.

Medications: Certain medications are absolute or relative contraindications to training. Patients with systemic hypertension taking ganglionic blocking agents should be excluded. The hypotension on standing at rest associated with further peripheral vasodilatation on effort may reduce coronary perfusion to a significant degree. A relative contraindication exists with the use of beta adrenergic blocking agents. Although beta adrenergic blockade simulates some of the effects of training (reduced exercising heart rate and decreased myocardial oxygen requirements),[11] it also causes depression of myocardial function.[12] If in fact a significant benefit of training in patients with coronary artery disease is a redistribution of peripheral blood flow to active muscle[13] and a decrease in myocardial oxygen consumption through a reduction in ejection time, heart rate and peripheral resistance,[14] inhibition of myocardial function would not appear to have a salutary effect and might negate other benefits. The use of digitalis, quinidine and other agents that alter the repolarization characteristics of the electrocardiogram could be considered relative contraindications only if the intent of training is in part to observe electrocardiographic improvement or exercise-induced changes in ischemic electrocardiographic thresholds.[15]

Systemic diseases: Several systemic diseases may significantly affect or contraindicate exercise. These include brittle insulin-dependent diabetes mellitus, cerebrovascular and peripheral vascular insufficiency, severe systemic hypertension and pulmonary emphysema when associated with hypoxia, hypercarbia and pulmonary hypertension. Exertional syncope or a history of hypotension also indicates undue risk.

Physical Examination

Careful examination of the cardiovascular system may disclose a patient at risk. Hyperthyroidism, congestive heart failure and abdominal aortic aneurysm are easily identified. A thorough preexercise cardiovascular screening attempts to identify more subtle lesions by particular attention to inspection, palpation of peripheral arteries, palpation and auscultation of the heart and close examination of the eye grounds.

A precordial thrill may indicate an acquired postinfarction ventricular septal defect or papillary muscle dysfunction. An apical impulse may indicate left ventricular hypertrophy or a ventricular aneurysm. A left parasternal impulse may indicate right ventricular hypertrophy of many causes or left atrial hypertension. All these conditions merit further clinical evaluation.

Cardiac auscultation is a critical part of the examination. Murmurs suggestive of acquired or congenital valvular disease must be identified. Patients with aortic stenosis of significant degree tolerate effort poorly, as manifested by exertional syncope and occasionally by sudden death. Similarly, subjects with aortic or mitral insufficiency have not been shown to benefit from training, and their marginal cardiac reserve may be threatened. Training may theoretically benefit patients with mild to moderate mitral valve stenosis.[10] In this lesion, the expected training effect of slowing of the submaximal heart rate and prolongation of diastolic filling period might reduce the end-diastolic mitral gradient. But training is not generally recommended as profitable for subjects with congenital or acquired valvular lesions.

Patients with severe systemic hypertension should be rejected for training. Such hypertension may be defined as a diastolic blood pressure greater than 120

mm Hg accompanied by advanced retinopathy. Although training can reduce diastolic pressure elevations of mild to moderate degree,[16] this reduction would not be expected in more severe hypertension.[17] The effects of exercise on fixed vascular resistance have not been defined clearly enough to exclude significant risk.

Laboratory Examinations

A limited number of laboratory procedures are essential to the careful preexercise screening. These consist basically of a resting electrocardiogram, a chest roentgenogram and blood chemistry determinations with special attention given to blood sugar, electrolytes and myocardial enzymes.

Electrocardiogram: Analysis of the electrocardiogram is probably the most important laboratory procedure. Evidence of increasing ischemia, unsuspected or clinically undetected infarction and specific arrhythmias and conduction disturbances contraindicate entrance into training. Ventricular arrhythmias, particularly multifocal premature ventricular beats, require delay of training and prompt treatment. Conduction disturbances such as complete right bundle branch block and left bundle branch block produce only insignificant hemodynamic changes in subjects without major coronary artery disease.[18–20] However, the occurrence of bundle branch block in acute infarction increases mortality[21,22] and is indicative of extensive myocardial damage. Therefore, the combination of bundle branch block and coronary artery disease indicates an added risk or contraindication to training.

Two specific conduction disturbances merit discussion because of their potentially lethal consequences during exercise. They are type II (Mobitz) second degree atrioventricular block and bilateral bundle branch block. In both, destructive infranodal lesions are assumed.[23–25] With exercise, the normally expected shortening of atrioventricular refractoriness does not occur and the accelerated atrial rate finds ventricular unresponsiveness.[26] Complete heart block has been documented on occasion when such rate increases occur,[27] and bilateral bundle branch block appears to be the most common electrophysiologic mechanism of complete heart block.[28]

Roentgenogram: X-ray examination of the chest for heart size represents another simple technique for identifying a subject with reduced cardiac reserve. Cardiomegaly of any cause requires investigation and may indicate extensive myocardial damage. The identification on X-ray or fluoroscopic study of coronary arterial calcification has been correlated angiographically and pathologically with severe atherosclerotic obstruction[29] and may indicate undue training risk.

Patient Benefit

The final screening analysis is concerned with the assurance of patient benefit. One can assume that benefit will occur if the subject has met the motivational, historical, clinical and laboratory standards described. However, training benefit is restricted to subjects with coronary artery disease; exercise programs in other forms of heart disease are both untested and potentially harmful. Therefore, the precise nature of the disease process causing ischemic pain must be known.

Patients may have angina pectoris without having coronary artery disease. This is dramatically seen in severe valvular aortic stenosis, idiopathic hypertrophic subaortic stenosis, other forms of cardiomyopathy and severe pulmonary hypertension, especially that due to mitral stenosis or occurring with congenital heart disease. Training programs in these conditions are not beneficial and may be lethal.

Conclusions

When thoughtful and carefully performed screening procedures are applied, few patients in organized training protocols will suffer. When basic guidelines for patient rejection are followed (Table III), risk is minimized, the subject is protected and the yield of good results should be enhanced.

There can be no substitute for adequate medical control and management of patients with coronary artery disease. These measures include treatment of increasing angina, control of the symptoms of heart failure and low cardiac output and treatment of coexisting systemic diseases. Before a patient enters a training program, his medications must be reviewed to ensure that their effects will not be reversed by exercise, and diseases producing ischemic pain and mimicking arteriosclerotic heart disease must be excluded. Finally, the patient must be properly motivated.

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Individual Exercise Prescription

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The ability to prescribe exercise for both normal persons and patients with heart disease has advanced from an art to a science during the past decade. Research during this period has given the physician and the exercise physiologist the capability of designing exercise programs to meet a specific person's individual needs, interests and capacity. In such programs, participants first undergo a thorough medical evaluation, including a detailed personal health and family history, physical examination, a resting 12 lead electrocardiogram and an exercise electrocardiogram. Either as part of the exercise electrocardiographic evaluation or as a separate exercise test, individual work capacity (either actual or estimated maximal oxygen uptake) and the maximal heart rate are determined.

In the actual exercise prescription, attention is given to four factors: (1) type of activity, (2) frequency of participation, (3) duration of each exercise period, and (4) intensity of the effort. To promote and maintain basic cardiorespiratory health and endurance, the exercise must be of an endurance nature—walk-jog-run, hiking, swimming or bicycling. It should be performed at least three times a week for 20 to 30 minutes at each session. Significant changes in work capacity and cardiovascular function occur when a person exercises at a level as low as 60 percent of his working capacity. A level of 60 to 75 percent is normally used to initiate an exercise prescription. This level can be easily monitored by the participant, using 60 to 75 percent of his maximal heart rate as the guide for his training or exercising heart rate. In all cases, the exercise is programmed to fit the individual subject, not vice versa, as often happens in group programs. This approach provides a safe and efficient means for assisting adults to gain maximal benefit from exercise.

The need to overcome effectively the sedentary habits of our adult population has been recognized for years. Physical inactivity has been intimately associated with obesity, premature cardiovascular disease, unnecessary orthopedic problems, anxiety and emotional tension. The man of today who is 40 years of age or older is definitely at greater risk of having the basic chronic degenerative diseases than his counterpart of 20 years ago. A part of this increased risk can be attributed to the basic inactivity of man today compared with man of that time.

Education and Motivation

Appreciating the need for increased physical activity and translating this need into action are, unfortunately, unrelated events. Any successful exercise program must therefore accomplish two major goals: (1) teach people why they should be physically active, and (2) motivate them to follow through with a personal activity program. The majority of existing exercise programs are short on education.

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TABLE I

Alterations in Endurance Capacity, Body Composition and Blood Lipid Levels in 44 Middle-Aged Men Consequent to a 3 Month Program of Prescribed Exercise*

Variable	Initial Mean†	Final Mean†	Change	% Change
VO_2 max (ml/kg per min)	28.2 ± 6.2	32.4 ± 6.3	+4.2	+14.9
Weight (kg)	81.4 ± 10.6	78.5 ± 10.2	−2.9	−3.6
Lean body weight (kg)	61.1 ± 6.1	61.8 ± 6.4	+0.7	+1.1
Fat weight (kg)	20.3 ± 6.2	16.7 ± 6.1	−3.6	−17.7
Relative fat (%)	24.5 ± 5.2	20.9 ± 4.9	−3.6	−14.7
Cholesterol (mg/100 ml)	246.2 ± 41.6	227.3 ± 41.5	−18.9	−7.7
Triglycerides (mg/100 ml)	145.8 ± 85.7	94.1 ± 40.3	−51.7	−35.5

* From the Preventive Medicine Center, Palo Alto, Calif.
† Mean ± standard deviation.

TABLE II

Alterations in Endurance Capacity, Body Composition and Blood Lipid Levels in 32 Middle-Aged Men Consequent to a 6 Month Program of Prescribed Exercise*

Variable	Initial Mean†	Final Mean†	Change	% Change
$\dot{V}O_2$ max (ml/kg per min)	37.9 ± 8.5	44.0 ± 7.6	+6.1	+16.1
Weight (kg)	80.5 ± 10.1	77.9 ± 9.6	−2.6	−3.2
Lean body weight (kg)	61.9 ± 6.7	62.9 ± 6.5	+1.0	+1.6
Fat weight (kg)	18.5 ± 6.7	15.0 ± 6.1	−3.6	−19.4
Relative fat (%)	22.7 ± 6.2	18.8 ± 6.0	−3.9	−17.2
Cholesterol (mg/100 ml)	257.1 ± 51.3	219.0 ± 40.4	−38.1	−14.8
Triglycerides (mg/100 ml)	131.0 ± 76.2	121.0 ± 92.8	−10.0	−7.6

* From the Adult Fitness Program, University of California, Davis, Calif.
† Mean ± standard deviation.

People are told that they *must* exercise but are given little if any information on *why* they should exercise. The average person today has a relatively sophisticated knowledge of the basic biological sciences and medicine. If he thoroughly understands the reasons for following a routine program of physical activity, he will be more inclined to do so. Probably the most valuable contribution made by Cooper[1] in his initial book Aerobics was to inform an educated audience specifically why exercise is essential to improving and maintaining health.

In addition to educating people, it is necessary to motivate them to act. Initially, much of this motivation can be in the form of external goals and rewards, but once a person has been actively exercising for several months or more, more subtle forms of internal motivation are needed. The individual man or woman must recognize that an exercise program is a lifetime pursuit and not an activity of 3 to 6 months' duration with residual effects that last forever.

Group programs provide excellent opportunities for motivation, teaching and interaction. The influence of the group and its leader or leaders has tremendous motivational significance. Unfortunately, group programs now involve a very small percent of our total adult population. Many people can't or won't take advantage of existing programs often for valid reasons. These people can be helped to develop their own personal exercise program. The remainder of this paper outlines the practical fundamentals of individualized exercise prescription for persons participating in organized groups or in programs designed specifically for them. The reader is referred to Pollock,[2] or Wilmore and Haskell[3] for a more extensive review of the theoretical aspects of exercise prescription.

Exercise Prescription

An individualized exercise prescription provides a practical answer to several problems. Most individual exercise programs are self-designed; that is, a man or woman selects an activity and begins exercising. This is a potentially dangerous practice since most people do not recognize their limitations and are likely to exceed a safe level of exercise. Just as important, people are likely to initiate an activity program without proper medical evaluation. A substantial number of persons have potential symptoms of cardiovascular disease—angina pectoris, for example—make a self-diagnosis, and with a fear of the physician confirming their diagnosis, embark on their own exercise program in an attempt to remedy the situation. Group programs also have associated problems. Although a medical examination may be required for participation in these programs, the exercise is usually prescribed on a mass basis and little or no recognition is given to individual differences: Everyone is expected to do exactly the same thing. The individualized prescription of exercise avoids these hazards. The participant receives medical clearance, his interests and physiologic capacity are individually determined, thus ensuring accurate prescription of an appropriate exercise regimen.

Medical screening: The first step in developing an individualized exercise prescription is to obtain proper medical evaluation.[4] The assessment should be based on a resting 12 lead electrocardiogram, a resting blood pressure determination, a blood lipid profile, a medical history providing pertinent information on past medical problems and familial traits, and a comprehensive physical examination performed by a physician with an understanding of the exercise sciences. Providing there are no contraindications, the participant is then cleared for the exercise test.

Exercise testing: The primary purpose of the exercise test is to determine the normality of the exercise electrocardiogram. In addition, measurements are made of the subject's ventilation, oxygen uptake, blood pressure and heart rate response to the exer-

cise. The work load is increased gradually until the subject reaches the point of fatigue or until clinical symptoms or electrocardiographic abnormalities appear that contraindicate continuation of the test. The plateau of oxygen uptake with an increasing work load indicates the attainment of the subject's maximal oxygen uptake or his physical working capacity. When equipment is not available to assess oxygen uptake, it can be estimated from the length of time of the exercise test. McDonough et al.[5] and Wilmore[6] have found correlations of 0.85 and 0.87, respectively, between maximal oxygen uptake and test duration in men, and Profant et al.[7] reported a correlation of 0.77 in women. The level of maximal oxygen uptake and the normality of the exercise response are the principal factors in the exercise prescription.

Body composition assessment: One additional component which is not essential for the prescription of exercise, but provides important medical and motivational data is the assessment of body composition. With use of either the hydrostatic weighing or the anthropometric estimate technique, lean body weight, relative and absolute body fat and ideal body weight can be estimated with a moderately high degree of accuracy. This assessment accurately identifies obesity, but, equally important, may motivate a participant to adhere to a prescribed dietary and exercise program.

Individualized prescription for exercise program: The actual prescription of exercise is given in an individual consultation immediately after the medical and physiologic evaluation. The prescription is based on: (1) the recommendation from the physician relative to the absence or presence of contraindicative medical problems; (2) a questionnaire on physical activity interests and habits; (3) results of the medical examination; and (4) results of the exercise test, including the actual or estimated maximal oxygen uptake. During the consultation, the results of the exercise stress test and the analysis of body composition are covered in detail. A personally tailored exercise program is then prescribed with attention being given to: (1) the type of activity; (2) the frequency of participation; (3) the duration of each workout; and (4) the intensity at which the activity is to be performed. Generally, an endurance type of activity of particular interest to the participant is suggested. The activity is to be performed three to four times a week for 20 to 30 minutes a day. The subject uses his pulse rate response to the exercise to control the intensity of his performance. He is told to exercise at a heart rate that represents 75 percent of his maximal oxygen uptake. This rate, termed the training heart rate, is well within his capability yet has been demonstrated to exceed the threshold necessary to elicit a training or conditioning response. This procedure applies, of course, only to persons who have no symptoms of heart disease. The training heart rate must be established individually. Use of a standard heart rate such as 150 beats/min for groups of persons all ages is a questionable procedure. This heart rate represents 75 percent of the capacity of the 25 year old but 98 percent of the capacity of the 65 year old and is independent of training state.[2]

The medical and physiologic evaluation and consultation are used as educational experiences. The subject receives explanations of most of the testing procedures and both written and verbal interpretations of his own test results. In addition, he should receive educational materials during the consultation and at various times throughout the year. Participants should also be given specific goals to reach within a specified time period. For example, a subject may be asked to increase his maximal oxygen uptake from 24 to 31 ml/kg per min and decrease his relative fat from 27.5 to 22.5 percent within 6 months. Additional long-range goals are also provided. Participants should be encouraged to return after 6 to 12 months for reevaluation. This procedure, intended to assess the success of the prescription, is also a valuable motivational tool for maintaining participants in an exercise program for the intervening 6 to 12 month period.

Results: The results from two programs using this approach to exercise prescription are presented in Tables I and II. The data in Table I represent changes after a 3 month exercise program and those in Table II after a 6 month program. In both cases, the changes are substantial and are all in the direction of improving the subjects' health profile. However, the changes in body composition and blood lipid levels cannot be attributed solely to the exercise program: many of the participants were also consuming modified diets prescribed by a dietician.

In summary, an individualized approach to the prescription of exercise has been shown to be both feasible and acceptable to the public. Programs based on this approach appear to provide meaningful changes in health. The two key factors in ensuring the success of an individualized program appear to be (1) provision of adequate education, and (2) generation of the motivation needed to carry out the immediate program with an appreciation that exercise is a lifetime pursuit.

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Effects of Physical Training on Coronary Risk Factors

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The effects of exercise training on the known coronary risk factors were studied as an isolated intervention in 39 middle-aged men who were at high risk of coronary artery disease. They were separated into two groups of 20 exercising and 19 control subjects who were carefully matched with respect to age, occupation, coronary risk factors and physical fitness. The exercising subjects participated in a 12 week, supervised training program, but no other attempt to reduce risk factors was made in either group.

Exercise training led to a substantial improvement in the physical fitness as determined by increased maximal oxygen uptake, oxygen pulse, ventilation and physical work capacity. Furthermore, there was a significant reduction of systolic blood pressure in the hypertensive subjects who exercised (from 148 to 135 mm Hg, $P < 0.01$) but not in the hypertensive control subjects (from 150 to 147 mm Hg); the diastolic pressure decreased in both groups. Hypertriglyceridemia also decreased in response to exercise, but there was no significant change in cholesterol levels, obesity, cigarette smoking or psychological profile. A physical training program is therefore valuable as adjunctive therapy in patients at high risk of coronary disease who have hypertension or hypertriglyceridemia.

Numerous reports over the past 20 years have drawn attention to the relation between physical inactivity and coronary artery disease. As a result, physical training programs have been widely advocated, and it has been inferred that participation in such programs would reduce the risk of and protect against coronary disease. This inference has been drawn primarily from two sets of observations: (1) epidemiologic studies showing that persons with more physically demanding occupations or leisure time activities generally have a lower rate of coronary artery disease than those who are more sedentary,[1–3] and (2) studies showing that the cardiovascular functional capacity of patients with coronary artery disease can be dramatically improved by physical training programs.[4–10] However, the role of physical training in the primary prevention of coronary disease or reduction of the mortality and morbidity from this disease has never been demonstrated.

Since coronary artery disease is caused by many factors, it is difficult to assess the individual impact or contribution of any single factor. This difficulty is further compounded when one attempts to assess the results of an intervention directed against that factor. But inferential evidence supporting the role of exercise training in primary prevention can be derived by the demonstration of a favorable influence on the major coronary risk factors. Thus, many authors have investigated the effects of training on serum lipids,[10–13] hypertension,[14–17] obesity[10,13] and psychological profile.[1,4,10,18] The reported

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results have varied and are often difficult to compare because the studies have been uncontrolled or several interventions were used concomitantly. Accordingly, a carefully matched and controlled study was undertaken to determine the effects of exercise intervention as an independent variable on hypertension, hyperlipidemia, obesity and cigarette smoking in a group of subjects at high risk of coronary artery disease.

Methods

Subjects. Forty untreated male volunteers with multiple coronary risk factors were identified from a heart disease screening program of policemen, firemen and sheriff's deputies in Sacramento. All underwent a complete physical examination with resting electrocardiogram, chest roentgenograms (posteroanterior and lateral views), maximal progressive treadmill stress tests with "on line" respiratory gas analysis, and a series of blood chemistry analyses. They were then separated into exercise and control groups which were closely matched with respect to age, occupation, coronary risk factors (hypertension, hyperlipidemia, obesity, cigarette smoking) and physical fitness (Table I).

The exercise group participated in a supervised physical training program, but no other effort to reduce risk factors was made during the course of this study. All subjects were specifically instructed to avoid alterations of diet and treatment of hypertension, and no attempt was made to have them discontinue cigarette smoking. In addition, the control group was asked to refrain from increasing their usual physical activities.

Blood pressure measurements: The blood pressure was recorded from both arms (at heart level) with a standard size cuff and mercury manometer while the subjects were seated. The arm with the highest pressure was used for subsequent blood pressure measurement, and at least three recordings, separated by more than 5 minutes, were taken during each of three examinations made before the start of the training program. The "pretraining" blood pressure was taken as the average of the three lowest readings during the third examination. All subjects in both groups had their blood pressure recorded in a similar manner at the midpoint and termination of the training program. All recordings were made by the same two physicians.

Lipid measurements: Serum cholesterol (automated method[19]) and triglyceride determinations (enzymatic method[20]) were obtained after a 14 hour overnight fast at the beginning and end of the training program. All of these measurements were carried out in duplicate by the same technician in the Lipid Laboratory of the University of California at Davis-Sacramento Medical Center.

Cardiovascular function capacity: Progressive multistage treadmill stress tests were carried out to the voluntary maximum using a standard protocol at the beginning, midpoint and conclusion of the training program. "On line" respiratory gas analysis (oxygen, carbon dioxide), ventilation (liters/min) and heart rate were measured every 15 seconds and strip chart recordings of the electrocardiogram were obtained at 1 minute intervals.

Psychological profile: A series of standard psychological tests, including a body image index[21] and adjective checklists that provide a personality profile and depression scale, were administered to all subjects at the beginning and end of the study.

Training program: The training program consisted of three exercise sessions (40 to 55 minutes each) per week (Monday, Wednesday, Friday) for 12 consecutive weeks. All sessions were conducted between 8 and 10 AM and were considered "regular duty." If a training session occurred on an "off duty" day, subjects were compensated for travel and training time at 1 1/2 times their hourly wage.

Each training session began with a 5 to 10 minute "warm up" period of light calisthenics and stretching exercises. This was followed by a 30 to 35 minute individualized period of walk-jog sequences during which the heart rate was maintained at a training level (70 to 85 percent of maximal rate), and this in turn was followed by a 5 to 10 minute "cooling off" period. The exercise sequences were paced by two physical educators, and two physicians carried out

TABLE I

Group Characteristics (means ± standard deviation)

	Control Group (no. = 19)	Exercise Group (no. = 20)
Age (mean and range) (yr)	43.1 (30–53)	41.3 (33–58)
Weight (lb)	204 ± 30	191 ± 20
Cigarette smokers (no.)	9	10
Blood pressure (mm Hg)		
Systolic	147 ± 16	138 ± 18
Diastolic	98 ± 8	92 ± 8
Cholesterol (mg/100 ml)	268 ± 60	260 ± 46
Treadmill duration (min)	11.3 ± 2.2	11.3 ± 2.5
Maximal oxygen consumption (cc/kg per min)	32.7 ± 5.4	33.4 ± 5.2
Triglycerides (mg/100 ml)	218 ± 109	243 ± 107

TABLE II

Effects of Training on Physical Fitness (means ± standard deviation)

	Control Group (no. = 19)	Exercise Group (no. = 20)
Maximal heart rate (beats/min)		
Pre	178 ± 16	178 ± 14
Post	178 ± 16	175 ± 14*
Treadmill duration (min)		
Pre	11.3 ± 2.2	11.3 ± 2.5
Post	11.6 ± 2.2	12.9 ± 1.6†
Maximal oxygen consumption (cc/kg per min)		
Pre	32.7 ± 5.4	33.4 ± 5.1
Post	33.2 ± 6.2	35.5 ± 5.1†
Oxygen pulse (cc/pulse)		
Pre	18.2 ± 2.1	18.4 ± 2.4
Post	18.7 ± 2.3	20.6 ± 2.7†
Ventilation (liters/min)		
Pre	93.1 ± 15.1	86.8 ± 12.7
Post	96.1 ± 16.0	95.5 ± 13.6†
Respiratory quotient		
Pre	1.07 ± 0.07	1.06 ± 0.06
Post	1.05 ± 0.07	1.05 ± 0.07

* $P < 0.01$.
† $P < 0.005$.

TABLE III

Effects of Training on Blood Pressure (means ± standard deviation)

	Mean Blood Pressure (mm Hg)	
	Systolic	Diastolic
A. Normotensive Subjects		
Control group (no. = 4)		
Pre	135	87
Post	132	78
Δ	−3	−9*
Exercise group (no. = 8)		
Pre	123	84
Post	126	78
Δ	+3	−6*
B. Hypertensive Subjects		
Control group (no. = 15)		
Pre	150	101
Post	147	90
Δ	−3	−11*
Exercise group (no. = 12)		
Pre	148	97
Post	135	83
Δ	−13	−14*

* $P < 0.01$

TABLE IV

Effects of Training on Serum Lipids (means ± standard deviation)

	Control Group (no. = 19)	Exercise Group (no. = 20)
Cholesterol (mg/100 ml)		
Pre	268 ± 60	260 ± 46
Mid	254 ± 38	226 ± 36
Post	274 ± 63	248 ± 51*
Triglycerides (mg/100 ml)		
Pre	218 ± 109	243 ± 107
Post	227 ± 119	187 ± 79*
• •		233 ± 146†

* 24 hours after exercise.
† 96 hours after exercise.

pulse rate and telemetric heart rate monitoring during the training periods. The exercise prescription was steadily increased as necessary to achieve the training heart rate during the program.

Results

Adherence: Thirty-nine of the original 40 subjects completed the study. One of the control subjects moved away from the area during this program and his data were deleted from the study. In the exercise group, 16 subjects (80 percent) attended more than 75 percent of the training sessions; the remaining 4 were present 60 to 75 percent of the time.

Physical fitness: Table II compares variables of cardiopulmonary fitness in the exercise and control groups before and after the training program. The exercise group had a significant reduction in their maximal heart rate and significant increases in their physical work capacity (treadmill duration), maximal oxygen consumption, oxygen pulse (maximal oxygen consumption/heart rate) and ventilation after training. The control group had no significant change in any of these measurements.

Blood pressure: Table III shows the changes in blood pressure in normotensive and hypertensive subjects. After the training program, normotensive and hypertensive subjects in both groups demonstrated a reduction in mean diastolic pressure. The reduction was statistically significant ($P < 0.01$) and similar in magnitude in hypertensive patients in the exercise and control groups. Systolic pressure was significantly reduced ($P < 0.01$) only in the hypertensive subjects who exercised.

Serum lipids: Serum cholesterol and triglyceride levels before and after the training program are shown in Table IV. There were no significant differences in cholesterol values within or between the groups. Triglycerides were significantly reduced in the exercise group when measured 24 hours after an exercise session but returned to base-line levels 96 hours after exercise.

Obesity, cigarette smoking and psychological profile: Although some subjects in both the control and exercise groups appreciably changed in weight during the course of the study, there were no significant differences in the mean weight of either group. No subject in either group discontinued or substantially decreased cigarette smoking during the program. Although all of the subjects who exercised claimed that they "felt better" after the training program, the psychological tests failed to demonstrate improvement in or differences between the groups.

Discussion

Our study demonstrates that a substantial improvement in cardiovascular and pulmonary functional capacity can be achieved by middle-aged, hypertensive, obese, hyperlipidemic, cigarette-smoking men engaged in a properly designed physical training program. This is shown by the significant increases in maximal oxygen consumption, oxygen pulse and ventilation and the concomitant increase in external work capacity (treadmill duration) associated with training. Furthermore, all levels of external work were carried out at a lower heart rate and rate-pressure product after training. The respiratory quotient (Table II) substantiates the fact that a maximal effort was made by the exercise and control groups during both testing periods; thus, differences between the groups cannot be attributed to motivation in the performance of a "voluntary maximum" stress test.[22] These results are in agreement with data from similar studies involving normal subjects and patients with coronary artery disease.[4–11]

Blood pressure: A most important finding was the demonstration of a significant reduction in the blood pressure of hypertensive subjects after exercise train-

ing (Table III). Although several authors[16,23] have shown that the blood pressure response to a given work load is less after training, the effects of training on resting blood pressure have been controversial. Although some investigators[14,15] claim that training has a salutary effect on hypertension, others[17,24] deny any significant change. However, these studies can all be faulted for the lack of an adequate control group, failure to segregate hypertensive from normotensive subjects or the associated use of other therapeutic interventions. Our normotensive subjects had mild decreases in diastolic pressure that were not statistically significant, a finding that is in agreement with other reported data. Hypertensive subjects in both the control and exercise groups had a significant reduction of diastolic pressure; thus, the observed diastolic changes in the latter group cannot be attributed directly to training. These changes may be the result of a reduction in anxiety associated with frequent contacts with the examiner and increasing familiarity during the course of the study.

Systolic blood pressure was significantly reduced only in the hypertensive patients who exercised. The mechanisms underlying this change are obscure. There is evidence that training results in decreased sympathetic tone and peripheral resistance in response to a given exercise stress,[23,25,26] and this also may be true for resting subjects. Whatever the mechanism, a substantial reduction of blood pressure was achieved in these hypertensive subjects in the absence of any other form of hypertensive therapy (drugs, sodium restriction or weight reduction).

Triglycerides and cholesterol: The serum triglycerides were substantially reduced when measured 24 hours after an exercise session but had returned to base-line levels when rechecked 96 hours after exercise. These results are in agreement with those of many published studies. Exercise as an isolated intervention (independent of diet) is an effective means of reducing serum triglycerides, but its effects are short-lived. Approximately three exercise sessions a week would be necessary to maintain the triglyceride reduction although it is obvious that dietary control should also be employed.

The reported effects of training programs on serum cholesterol values have varied.[10–13] However, most studies indicate little or no change in cholesterol in the absence of dietary fat restriction or significant weight loss. If one considers only the base-line and midpoint values (after 6 weeks of training) for cholesterol, both the exercise and control groups demonstrated a "reduction," whereas neither group showed a statistically significant change after 12 weeks. These results underscore the problem of day to day cholesterol variability and the need for multiple determinations in any study of cholesterol changes.

The lack of a significant weight reduction in the exercising subjects is not surprising since we specifically recommended that they not change their dietary habits during this program. Most other studies that have not imposed this restriction have found minor weight reduction or an increase in lean body mass, or both. Our groups had no changes in mean values for lean body mass as determined by skin-fold thickness measurements.

Although our exercising subjects were uniformly enthusiastic over their improved physical prowess during this program, no one was sufficiently motivated to reduce cigarette consumption. It was surprising that there was no demonstrable improvement in the psychological profile of our exercise group since these subjects all claimed that they "felt better" and were proud of their improvements in physical performance. The lack of measureable improvement in results of adjective checklists and body image indexes may be a function of our group selection. All subjects were either law enforcement officers or firefighters who might be expected to be less likely than other groups to acknowledge initially a poor body image or emotional insecurity.

In summary, exercise training improves cardiovascular functional capacity in subjects at high coronary risk and favorably influences hypertension and hypertriglyceridemia but has no appreciable effect on the other coronary risk factors evaluated here. A program of regular exercise is therefore a valuable form of adjunctive therapy in patients at high coronary risk who have hypertension or hypertriglyceridemia. It has not been established that such a program will in fact prevent or reduce the risk of developing coronary artery disease, but that would be a logical inference from the available data.

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Long-Term Physiologic Adaptations to Exercise with Special Reference to Performance and Cardiorespiratory Function in Health and Disease

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The exercise training principles of specificity, overload, individual differences and transiency are discussed and examples of each presented. Disadvantages of the cross-sectional method, and the values of the longitudinal method of ascertaining physical training effects are discussed. The effects of endurance-oriented exercise programs on middle-aged sedentary normal men and patients with coronary artery disease, emphasizing body composition and cardiorespiratory function and basic hemodynamic response to submaximal and maximal exercise, are reviewed. An original study of the effects of endurance-oriented training on patients after myocardial infarction and coronary artery bypass is presented. Emphasis is placed on cardiorespiratory function at submaximal and maximal exercise loads, and the patients' response is contrasted to that of a group of sedentary normal subjects of similar age.

It is concluded that after infarction most trained patients can achieve the performance levels of sedentary normal subjects but that their response to training is often restricted, presumably because residual disease effects myocardial dysfunction. Successful coronary artery bypass surgery seldom normalizes work performance and cardiorespiratory function although it may ameliorate symptoms. Physical training in conjunction with bypass surgery effects a further improvement in work performance and aerobic power.

The long-term effects of systematic physical exercise have been subjected to scientific investigation for at least 60 years. The first comprehensive review was completed by Steinhaus in 1933[1]; more recent discussions are included in exercise physiology textbooks, the most complete being that by Åstrand and Rodahl.[2]

Participation in properly designed exercise training programs increases capacity for muscular work by effecting morphologic and functional changes. These include (1) increased muscular strength and endurance, primarily as a result of enlargement of existing muscle fibers and an increase in the number of capillaries; (2) better neuromuscular coordination, which reduces the energy requirement; (3) altered body composition, generally involving an increase in muscle mass and a decrease in adipose tissue; and (4) increased maximal oxygen uptake, due primarily to increases in blood volume, total hemoglobin, heart size and stroke volume, and a widened arteriovenous oxygen difference. The effects of training on other body systems, and their relative importance to increased physical performance, are not well known.

Until recently, the effects of physical training were frequently attributed to differences between athletes and nonathletes. This suppo-

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sition is not entirely valid since athletes are genetically endowed according to the particular requisites of their sport[3] and the distinction between constitutional dissimilarities and the effects of physical training is not amenable to definitive analysis. Primarily for this reason it is preferable to use the longitudinal approach, in which subjects are followed up over an appropriate period of time. Although this method is not without objections from a scientific viewpoint,[2] with proper attention to subject sampling procedures, insistence on stable habitual life patterns during the investigation, motivation, careful monitoring of the intensity of the training program, and appropriate control groups, it is preferred. It has been demonstrated, however, in numerous epidemiologic, cross-sectional investigations that physically active men are less likely to have myocardial infarcts, and when they do, are less apt to die.[4] Although these studies have inherent weaknesses in design, they have provided impetus for the longitudinal investigation of exercise programs on work performance and physiologic variables related to coronary artery disease risk factors in middle-aged normal subjects. Within this context, the effects of physical training on work performance and cardiorespiratory function in health and disease are reviewed.

Principles of Physiologic Adaptation to Training

Specificity of training: Exercise training programs can be biased to achieve particular physiologic effects. Obviously, the effects of a weight training regimen are quite different from those achieved by gradually intensified jogging. But even within a particular activity, there are specific effects. For example, Clausen and Trap-Jensen[5] trained two groups to perform dynamic work on a bicycle ergometer, one group using the arms only and one using leg work only. The reduction in heart rate obtained by training the arm muscles only could not be transferred to an ergometer leg work task, and vice versa. Thus, it was concluded that local changes in the trained muscles are of importance for the effect of training on heart rate. A recent study[6] of female twins with a similar level of maximal oxygen uptake demonstrated that the twin who had continued to engage in competitive freestyle swimming training used a much greater percentage of her maximal oxygen uptake and sustained a significantly faster swimming pace than the twin who had remained active but had given up swimming training 3 years previously. The difference in maximal oxygen uptake was less pronounced in arm ergometer work, and it was concluded that the continued swimming training had, by unknown mechanisms, enabled one twin to achieve close adaptation of central and peripheral functions to the specific work of swimming.

Proper training may increase the size and, some evidence suggests, the number of myofibrils within a muscle fiber. This appears to be primarily the result of a strength training stimulus that affects particularly the white fibers. Utilization of a high resistance, low repetition training program in lifting weights is the most effective method for increasing muscle size and strength. On the other hand, utilization of a low resistance, high repetition program produces an endurance training stimulus that increases the number of capillaries, muscle mitochondria, energy-liberating enzymes in the sarcoplasm and electron transport capacity.[7]

Improved efficiency in terms of reduced energy expenditure is another training effect specific to the particular activity engaged in. Brouha's studies[8] indicate that through training and practice in activities requiring mastery of skills (such as skiing and swimming), energy expenditure is reduced by (1) elimination of unnecessary dynamic and static muscular contractions, (2) more complete relaxation of muscular antagonists, and (3) replacement of voluntary movement with reflex action. In activities that are uncomplicated technically, such as walking, there is no noticeable increase in efficiency as reflected by reduced oxygen consumption.

Overload: Both intensity and duration are important factors influencing the degree of training effect. Depending on the particular requirements of their sport or event, athletes generally use maximal or near-maximal efforts at appropriate rates and duration to enhance the rapid achievement of specific training effects.[7] However, when training middle-aged men, one is more concerned with the training threshold in achieving an optimal intensity. Karvonen[9] demonstrated a reduction in both work and resting heart rates when previously untrained medical students ran on a treadmill for 30 minutes 4 to 5 days per week with speed adjusted to attain a heart rate at 60 percent of the difference between the maximal and resting rates. At lower rates, the training effect was not seen and the speed of running had to be increased for further improvement. The combined effect of intensity and duration may be observed in Figure 1. Initially, a rather rapid decrease in blood lactate was effected, but was followed by a leveling

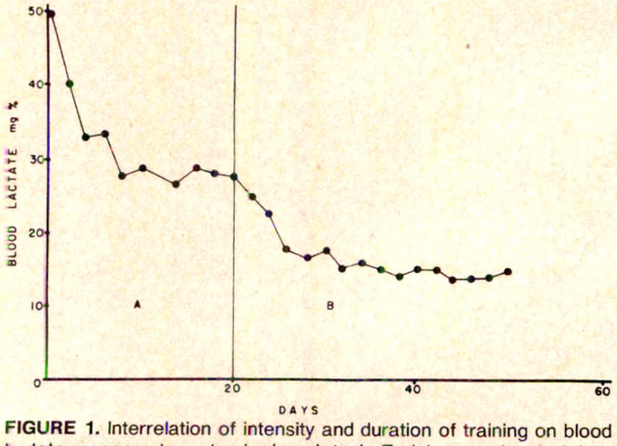

FIGURE 1. Interrelation of intensity and duration of training on blood lactate response to a standard work task. Training consisted of daily running on the treadmill for 20 minutes at 7 miles/hour for 20 days, followed by 15 minutes at 8.5 miles/hour for 30 days. (Reproduced by permission from Brouha.[8])

TABLE I

Comparison of Changes in Maximal Oxygen Uptake ($\dot{V}O_2$ max) with Training in Middle-Aged Men

	Pollock et al.[17]	Tzankoff et al.[23]	Naughton & Nagle[24]	Mann et al.[25]	Hanson et al.[26]	Saltin et al.[27]	Pollock et al.[18]	Oscai et al.[28]	Ribisl[29]	Wilmore et al.[30]	
Subjects (no.)	16	15	18	62	7	50	22	14	15	16	7
Mean age (yr)	49	54	41	25–60	49	43	39	37	40	40	53
$\dot{V}O_2$ max (ml/min per kg)											
Before training	29.9	30.2	31.3	34.0	35.1	36.0	37.1	38.5	40.1	40.1	40.3
After training	38.9	36.1	36.8	39.6	40.7	42.5	43.3	47.0	45.5	44.1	41.8
%Δ	30	20	18	16	16	18	17	22	14	10	4
Training duration (wk)	20	25	30	24	28	8–10	20	20	20	10	10
Frequency (sessions/wk)	4	2.3	3	5	3	2–3	2	3	3	3	3
Work time/session (excluding warm-up) (min)	40	55	30	40	60	20	45	30	35	12–24	12–24
Work intensity (% of maximal heart rate)	70	—	—	250–850 kcal/hour	—	90+	85	88	300–750 kcal/hour	600–700 kcal/hour	
Type of activity	Walk	Games, walk, jog	Run, calis-thenics	Calis-thenics, walk, run	Run, games, calis-thenics	Run, walk, calis-thenics	Run	Run	Run, calis-thenics	Jog	

off after 20 days until the training speed was increased to 8.5 miles/hour, and a further progressive decrease occurred for 10 days before again leveling off.[8]

In the training of middle-aged men, Siegel and coworkers[10] postulate that the number of sessions a week, the total duration of training, the effective duration of each session and the intensity of exercise influence the degree of improvement. They found that training at an intensity necessitating a heart rate slightly in excess of 80 percent of predicted maximal rate, performed 2.6 times a week for an effective total of 30 minutes a week for 15 weeks, resulted in a significant increase in maximal oxygen uptake. The improvement was not maintained by continuing training for 10 effective minutes 0.9 sessions a week.

Individual differences: The response of a subject to a training stimulus is affected by his genetic potential, age and level of physical activity immediately before training. An inverse relation between the initial level of maximal oxygen uptake and percent improvement is shown in Figure 2.[11] Despite their relatively lower initial values, middle-aged men appear to be less trainable than younger subjects. The importance of the pretraining activity level is strikingly portrayed in Figure 3.[12] In three previously sedentary subjects, maximal oxygen uptake increased from an initial value of 2.52 to 3.41 liters/min (35 percent) with 55 days of hard aerobic training, whereas in the two previously active subjects it increased from 4.48 to 4.65 liters/min (4 percent). However, starting with the bed rest value after 21 days, the increases were

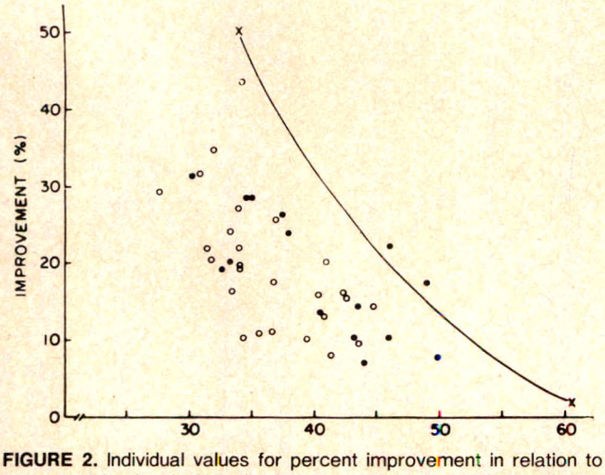

FIGURE 2. Individual values for percent improvement in relation to the pretraining level of maximal oxygen uptake in middle-aged men; the mean value for young men is included as a line. (Reproduced by permission from Saltin.[11])

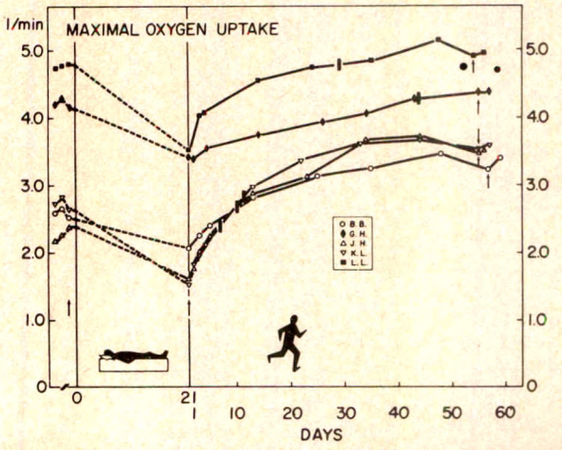

FIGURE 3. Changes in maximal oxygen uptake with bed rest and training. The **heavy bars** indicate the time during the training period at which the maximal oxygen uptake had returned to the control value before bed rest. Subjects G.H. and L. L. were in a trained state at the initiation of the experiment. (Reproduced by permission from Saltin et al.[12])

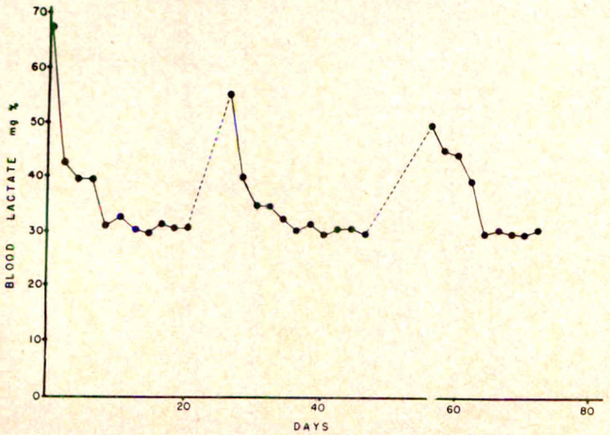

FIGURE 4. Effect of stopping exercise for a few days during a training period on blood lactate response to running on a treadmill for 10 minutes at 7.5 miles/hour. The dotted lines indicate two periods during which no exercise was performed. (Reproduced by permission from Brouha.[8])

from 1.74 to 3.41 liters/min (96 percent) and 3.48 to 4.65 liters/min (34 percent), respectively. If the bed rest were necessitated by disease processes in a vital organ, the deterioration in physical working capacity would be even greater. Furthermore, even if physical working capacity were known before the onset of disease, it would be difficult to ascertain the diminution due to disease compared to that caused by inactivity.[2]

Transiency of training: Most training studies have not been carried beyond several months duration. A notable exception is that of Katila and Frick,[13] who noted increased performance and lower submaximal heart rate in six subjects after 2 months of programmed training. Three subjects continued to train for 2 years and exhibited further training effects, whereas those who ceased training demonstrated exercise tolerance and heart rate characteristic of their pretrained state. Return to original pretraining values after cessation of training for 14 weeks has been observed.[10] In fact, significant training reversal may be a matter of several days, as is suggested in Figure 4.[8]

The longitudinal study of nine college cross-country runners provided an opportunity to assess the interrelated effects of increased maturity, work load (in terms of intensity and distance run), duration and transiency of training. After 3 months of training and competition, their maximal oxygen uptake increased from 62.1 to 66.6 ml/min per kg.[14] Six runners continued training and, when tested at peak training form 1 to 4 years later, demonstrated a further increase of 6.5 ml/min per kg to 72.0. They had no significant change in body weight during this period. Two of the three who ceased active training and were available for subsequent study had an initial maximal oxygen uptake of 61 ml/min per kg, which increased to 64.6 during training, but then regressed to 58.7 when measured 2 to 3 1/2 years later. These subjects gained approximately 10 percent of body weight during the period of nontraining.

Selected Effects of Endurance-Oriented Training on Normal Middle-Aged Men

Body composition: Physical training has a potentially profound influence on man's body composition, both increasing muscle mass and decreasing fat. However, since K^{40} has been found to be relatively constant in adults over a long period of time, some researchers maintain that change in body composition in the adult population is due to reduction in fat alone, and rarely to increased muscle mass.[15] Moreover, it is unlikely that substantially increased muscle mass is effected by rhythmic, relatively low resistance exercise characteristic of most middle-aged adult physical training programs. Conversely, the energy expenditure of walking, jogging or running over a speed range from 4.6 to 16 km/hour necessitates between 1.4 to 1.7 kcal/kg of body weight per mile traversed,[16] and could result in substantial fat loss.

Longitudinal studies on changes in body composition effected by physical training in middle-aged men have been summarized by Pollock et al.[17] In programs primarily entailing jogging 2 to 4 times a week for periods up to 1 hour for 10 to 24 weeks, the average loss in body weight was 1.4 kg and the mean decrease in percent of body weight as fat was 1.3. Apparently the amount of training is more important than intensity, in that training at 80 to 90 percent of maximal heart rate for 45 minutes 2 days a week for 20 weeks did not cause significant changes in body composition.[18] However, a saturation point apparently occurs, since subjects who trained 30 to 35 minutes for 2 to 3 days a week for 2 years revealed reductions of 3.8 percent of body weight after 6 months and 5.5 percent after 12 months but had no additional change thereafter.[19]

Cardiorespiratory effects: The primary measure of the quality of the cardiorespiratory system is $\dot{V}O_2$ max, which is the product of cardiac output and arteriovenous oxygen difference and reflects both the performance of the heart as a pump and the efficiency of blood flow distribution and oxygen utilization.[20] For young untrained men, the mean value is approximately 50 ml/min per kg, which diminishes with age to about 30 ml/min per kg at age 70.[21] Values as high as 85 ml/min per kg have been noted in highly trained Olympic cross-country skiers and distance runners.[22]

Endurance-oriented physical training of middle-aged subjects for several months increases maximal oxygen uptake. The degree of increase appears to be an interrelation of age, activity level before training, and the intensity and duration of training (Table I; Fig. 2 and 3), but accurate definition of the relative importance of each is presently lacking. Maximal heart rate is either unchanged or slightly lower, whereas oxygen pulse and pulmonary ventilation are increased.[2] The increase in pulmonary ventilation is proportional to that in $\dot{V}O_2$ max, and since arterial blood gas studies indicate that ventilation and diffusion do not limit maximal performance under normal conditions, improvements secondary to training must primarily involve the circulation.[26] In young men this

improvement may occur both by enlargement of cardiovascular dimensions (particularly heart volume, blood volume and total hemoglobin) and by improved function of the circulation itself, although the length of training appears critical to the former.[12]

At submaximal work loads in activities such as walking or riding a bicycle ergometer, there is no appreciable increase in skill with training and, thus, no reduction in oxygen consumption. There is, however, reduced physiologic strain as evidenced by a decreased percent of maximal oxygen uptake at submaximal work loads, and by absolute decreases in heart rate, pulmonary ventilation, blood lactate and ventilatory equivalent.[23,26,31] The reduction in submaximal heart rate is normally associated with an increased stroke volume and perhaps better vasomotor adjustments of blood flow to the working muscles, as is suggested by slightly reduced systemic blood pressures.[23] Because of this improved efficiency, work load capacity at a particular heart rate is augmented.[26] Since cardiac output and oxygen carrying capacity of the blood at submaximal work are the same, or nearly so, improved ventilatory efficiency appears to be due to peripheral factors. The lower level of blood lactate in submaximal work may be due to better distribution of the blood flow or possibly to an increased activation of red muscle fibers with a more efficient energy yield from aerobic processes.[27] The biochemical mechanisms by which this could occur have been established by Holloszy[32] but were derived from animal experiments. More recently, Kiessling et al.[33] have demonstrated that previously sedentary young men who ran 12 miles a week for 28 weeks increased the number of muscle mitochondria. More severe training, as evidenced by the study of elite endurance athletes, showed little difference in the number of mitochondria, but a pronounced size increase as compared to the trained normal young men. Further evidence of the peripheral cardiorespiratory changes effected by training is afforded by Varnauskas and co-workers,[34] who observed a 44 percent increase in succinic dehydrogenase activity (an enzyme probably present only in the mitochondria).

Hemodynamic response: After training, cardiac output is unchanged[35] or slightly reduced during submaximal work.[26,36] Although there is a widened arteriovenous oxygen difference with training in young men,[11] both an increase at greater submaximal work loads[26] and no difference[35] have been noted after training in middle-aged men. Slightly reduced mean systemic arterial blood pressure at submaximal work loads in middle-aged men after training has been observed.[23,35] Since cardiac output is little changed and heart rate and mean blood pressure are reduced at submaximal work, the reduced pressure must indicate that the contractile work of the left ventricle declines slightly.

There is a paucity of data on hemodynamic responses after physical training at maximal exercise levels in normal, middle-aged men. Hence, the hemodynamic response at maximal performance in young men who have undergone endurance training is summarized in Table II. The 15.4 percent increase in maximal oxygen uptake is the result of a nearly equal increase in both arteriovenous oxygen difference and cardiac output. The increased cardiac output was entirely effected by a greater stroke volume, since maximal heart rate was reduced 3 percent. Hartley et al.[35] studied the hemodynamic effects of training on middle-aged men during maximal work, and observed a 14 percent increase in maximal oxygen consumption which was almost entirely the result of increased cardiac output. There was no significant difference in arteriovenous oxygen difference and, since heart rate was slightly reduced, the increased cardiac output and maximal oxygen uptake were entirely a function of a 16 percent increase in stroke volume. There is a close relation between stroke volume and heart volume in young men, which has also been observed in middle-aged, still-active athletes.[38] Both stroke volume and heart volume increase with training in young men,[12] whereas in sedentary, middle-aged men the stroke volume was lower than would be expected from their heart volume, but increased with training concurrent with no change in heart volume,[35] thus suggesting possible improvement in myocardial contractility.

TABLE II
Summary of Findings During Maximal Work in Three Longitudinal Studies on Hemodynamic Effects of Training in Sedentary Young Men (from Saltin[11])

	Max $\dot{V}O_2$ (liters/min)	a-$v\bar{O}_2$ diff (Vol %)	$\dot{Q}$ (liters/min)	HR (beats/min)	SV (ml)
Minneapolis[37] (no. = 6)					
Control	3.42	15.1	22.8	193	118
Training	3.87	16.3	23.8	186	128
Diff (%)	+13.2	+8.0	+4.4	−3.6	+8.5
Stockholm[36] (no. = 8)					
Control	3.10	13.8	22.4	200	112
Training	3.44	14.3	24.2	192	127
Diff. (%)	+11.1	+3.6	+8.0	−4.0	+13.4
Dallas[12] (no. = 3)					
Control	2.52	14.6	17.2	192	90
Training	3.41	17.0	20.0	191	105
Diff. (%)	+35.3	+16.4	+16.4	−0.5	+16.7
Mean (no. = 17)					
Control	3.11	14.4	21.5	196	110
Training	3.59	15.5	23.2	190	122
Diff. %	+15.4	+7.6	+7.9	−3.1	+10.9

a-$v\bar{O}_2$ Diff = arteriovenous oxygen difference; HR = heart rate; Max $\dot{V}O_2$ = maximal oxygen consumption; $\dot{Q}$ = cardiac output; SV = stroke volume.

Mazzarella and Jordan[39] examined the possibility of reversing ischemic electrocardiographic exercise responses in seven middle-aged sedentary men who were asymptomatic at rest by subjecting them to 20 minutes of walking three times a week for 8 to 10 weeks. Six men showed less S–T segment depression

TABLE III

Basic Characteristics of Subjects

	Sedentary Normal (no. = 45)	Trained After Infarction (no. = 11)	Postoperative Bypass	
			Untrained (no. = 17)	Trained (no. = 4)
Age (yr)				
Mean ± 1 SD	50.0 ± 5.8	47.6 ± 8.0	50.6 ± 5.6	53.7 ± 8.2
Range	38.9–60.3	38.4–60.9	42.3–62.0	45.0–62.0
Height (cm)				
Mean ± 1 SD	178.9 ± 7.2	175.2 ± 4.8	174.7 ± 4.8	175.3 ± 3.5
Range	165.0–190.2	165.7–182.1	165.4–184.2	171.6–179.4
Weight (kg)				
Mean ± 1 SD	81.3 ± 11.4	74.9 ± 7.6	77.4 ± 9.5	71.4 ± 6.8
Range	63.9–103.4	62.8–85.5	64.0–94.6	64.0–78.4
BSA (m^2)				
Mean ± 1 SD	1.98 ± 0.2	1.89 ± 0.1	1.91 ± 0.1	1.85 ± 0.1
Range	1.70–2.28	1.67–2.03	1.75–2.18	1.75–1.94

in submaximal work after training, five showed improvement at maximal exercise, and only three exhibited S–T segment depression in their immediate postexercise electrocardiogram.

Adaptation to Endurance-Oriented Training in Coronary Artery Disease

With impetus provided by the early work of Hellerstein et al.,[40] physical reconditioning has in the past decade become part of the armamentarium of treatment for patients with coronary artery disease. Several investigators[41–45] have shown that many patients with coronary artery disease can be retrained to perform better than sedentary normal subjects of similar age, although until recently the mechanisms effecting this improvement were not well elucidated.[46] The variability of response to physical training is greater in patients with coronary artery disease, presumably because the severity of the underlying disease limits some patients' ability to respond to the training stimulus.[41,47]

Angina pectoris: Although MacAlpin and Kattus[48] have demonstrated "walking through angina," most investigators have stopped such patients from exercising to the point of maximal effort because of pain; that is, they were symptom-limited.[49] Undoubtedly this procedure underestimates maximal work capacity, since an increase of 14.5 percent in maximal oxygen uptake has been observed in patients with angina after sublingual administration of 0.4 mg of nitroglycerin.[50] Detry and Bruce[51] observed increased maximal oxygen uptake (symptom-limited) after training, and others have noted a greater amount of work before onset of pain, which suggests decreased cardiac oxygen consumption or increased coronary blood supply, or both.[46,52] In addition, Redwood et al.[52] have made observations at the onset of angina that indicate that training might improve myocardial oxygen delivery. In submaximal work, heart rate, mean blood pressure, pressure-rate product, tension-time index and presumably myocardial oxygen requirements are reduced.[5,52–54] In addition, reduced S–T segment depression has been noted.[40,51] Hemodynamic studies have revealed little or no change in cardiac output with a concurrent increase in stroke volume and nearly constant arteriovenous oxygen difference,[53,54] whereas reduced muscle blood flow and a widened arteriovenous oxygen difference at low work loads[55] and increased muscle blood flow at heavier loads of submaximal work[5] have been observed. The latter finding suggests that peripheral factors may also improve myocardial performance, as has recently been substantiated by Detry and Bruce,[51] who found no difference in the tension-time index, S–T segment depression relation at symptom-limited levels of maximal oxygen uptake after training.

Myocardial infarction: Relatively few studies have been made of the effects of physical training on patients after myocardial infarction without significant concurrent angina. Early studies of such patients[40,42–44,47] demonstrated reduced heart rate, S–T segment depression and decreased indirect blood pressure and tension-time index at submaximal work loads. A variety of exercise programs, including walking, jogging, ergometer cycling and endurance calisthenics and games, involving sustained energy expenditures of up to 7 kcal/min (oxygen consumption 1.4 liters/min) for periods of 1 hour, three to five times a week, were utilized in these studies. Increased physical performance has also been demonstrated,[42,43] as has increased maximal oxygen uptake.[41,45]

Comparison of submaximal and maximal cardiorespiratory function of patients after myocardial infarction and coronary bypass grafting with function in sedentary normal subjects: To test safely patients with various degrees of cardiac dysfunction, a slowly progressive multistage treadmill test that permits determination of maximal performance and attendant submaximal and maximal cardiorespiratory responses was developed.[56] The test is initiated at a speed of 50 meters/min, zero grade, and the work load increased every 3 minutes,

first by increasing the speed 10 meters/min to a maximum of 80 meters/min, and then by increasing the inclination 2 percent to a maximum of 22 percent at 42 minutes. Exercise is continued to the point of maximal tolerable effort as defined by dyspnea, leg weakness or electrocardiographic contraindication. Heart rate is recorded periodically, whereas oxygen consumption and associated respiratory metabolism measures are derived by standard procedures from data collected by open circuit metabolism.[56]

A community search revealed 11 men who had trained for 6 months to 11 years after myocardial infarction. Ten were jogging 30 to 45 minutes 3.5 times a week, and one patient swam 45 to 60 minutes, 5 times a week. Subsequently, 17 untrained men were studied 5 to 19 months after single or multiple aorto-coronary bypass grafts. Thirteen had postoperative angiograms to confirm graft patency. One patient continued to have left ventricular failure with patent grafts, two patients had one of two grafts blocked, and one patient with residual angina had occlusion of his single anterior descending artery bypass. Forty-five sedentary normal men of similar ages (Table III) were used for comparative purposes. Student's t test was applied to determine if the mean differences between either of the two patient groups and the sedentary normal group were significant ($P = <0.05$). The comparisons of maximal performance and of submaximal and maximal cardiorespiratory function of the patient groups have inherent limitations and bias: (1) The subjects trained after infarction were not available for study before infarction or training; (2) subjects trained after infarction and those who had undergone coronary artery bypass are not strictly comparable because of differences in severity of disease and training; and (3) subjects trained after coronary artery bypass were not tested preoperatively since assessment of maximal tolerable effort did not seem justified before operation. Within these limitations, however, certain comparisons of the patient groups with the sedentary normal group are informative.

All subjects completed the first seven work loads (stages) encompassing 21 minutes, and only one subject who had undergone coronary artery bypass surgery failed to attempt stage 9 (80 m/min, 10 percent grade), which was accepted as the upper end of submaximal work. Graphic analysis of submaximal data in the three groups is shown in Figures 5 to 7. The close similarity in oxygen consumption values for all groups at submaximal work loads indicates that there was no significant difference in walking skill. Apparent differences between the patients trained after myocardial infarction and normal groups in heart rate, oxygen pulse, pulmonary ventilation and ventilatory equivalent were not statistically significant. On the other hand, differences in pulmonary ventilation and ventilatory equivalent between the normal group and patients who had undergone coronary artery bypass were significantly different over the whole range of submaximal work; values for heart rate and oxygen pulse were significantly different after 15 minutes.

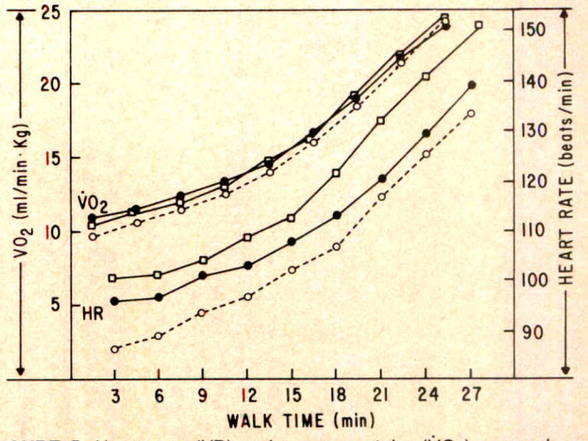

FIGURE 5. Heart rate (HR) and oxygen uptake ($\dot{V}O_2$) comparisons between a sedentary normal group and two groups with coronary artery disease at submaximal work loads. ● = sedentary normal; ○ = trained after infarction; □ = untrained after bypass surgery.

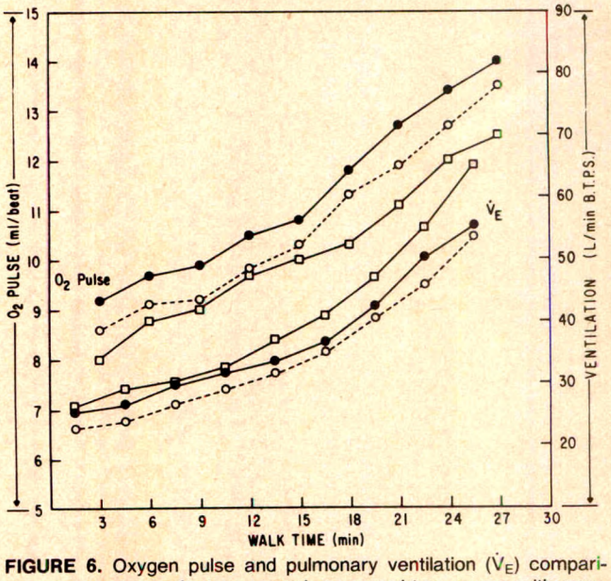

FIGURE 6. Oxygen pulse and pulmonary ventilation ($\dot{V}_E$) comparisons between a sedentary normal group and two groups with coronary artery disease at submaximal work loads. ● = sedentary normal; ○ = trained after infarction; □ = untrained after bypass surgery.

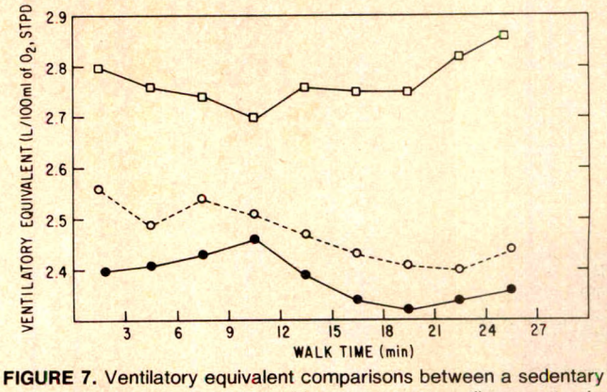

FIGURE 7. Ventilatory equivalent comparisons between a sedentary normal group and two groups with coronary artery disease at submaximal work loads. ● = sedentary normal; ○ = trained after infarction; □ = untrained after bypass surgery.

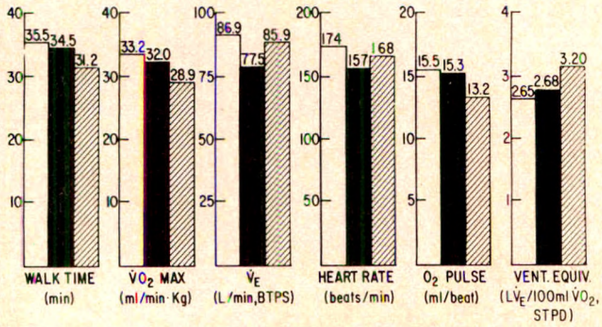

FIGURE 8. Comparisons of maximal performance data between a sedentary normal group and two groups with coronary artery disease. □ = sedentary normal; ■ = trained after infarction; ▨ = untrained after bypass surgery.

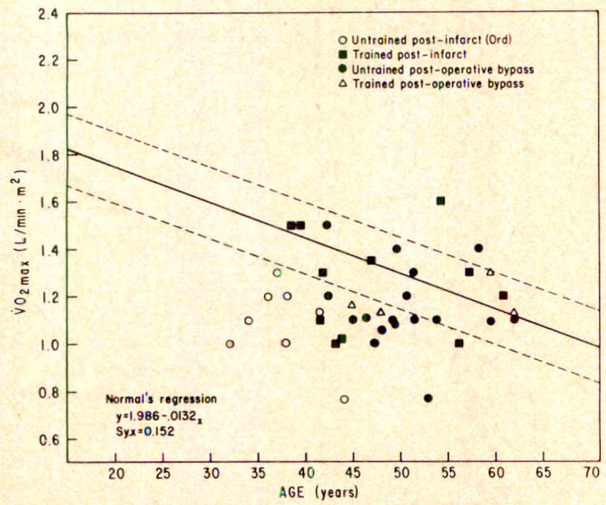

FIGURE 9. Individual values for untrained and trained subjects after myocardial infarction and coronary artery bypass. The **solid line** indicates the regression line for a sedentary normal group; the **dashed lines** represent 1 standard deviation above and below the regression line of the normal subjects.

Mean values for walking time and selected cardiorespiratory responses at maximal tolerable effort for the three groups are summarized in Figure 8. The group values for patients trained after myocardial infarction were similar to those of normal subjects except for significantly lower heart rate and pulmonary ventilation. In four subjects in the former group, maximal efforts should be considered symptom-limited; one patient had angina, one had leg cramps and two had marked ischemic S–T segment depressions and were stopped by the examiner before there was a clear tendency of the oxygen consumption to plateau. On the other hand, all of the coronary artery bypass patients walked to maximal effort, as evidenced by plateauing of oxygen consumption. Nevertheless, compared with the normal subjects, these patients had significantly shorter walking time, lower maximal oxygen uptake, heart rate and oxygen pulse and a higher ventilatory equivalent. Electrocardiographic evidence of myocardial ischemia increased with effort in five patients, four of whom had patent grafts as assessed by angiography. Seven had no change in resting ischemic electrocardiographic changes with effort; the remaining five exercised to maximal level with normal tracings.

Cardiorespiratory adaptation to training after coronary artery bypass: Four of the subjects studied after coronary artery bypass surgery consented to enter a quantitative reconditioning protocol, training at least 3 days a week, 40 minutes a day for 12 weeks by walking and jogging at an intensity necessitating a heart rate of 75 to 85 percent of maximum. Data after training (Table IV) indicate no appreciable change in oxygen consumption in submaximal work, but heart rate in the later work stages increased 4 to 6 beats/min. As a result, the oxygen pulse after training was somewhat lower. Submaximal pulmonary ventilation was essentially the same after training, whereas the response to training of ventilatory equivalent was variable. Clearly, there were no classic training ef-

TABLE IV

Effect of Training 12 Weeks on Cardiorespiratory Function in Four Coronary Artery Bypass Surgery Patients

Variable	Stage 1(0–3:00)		Stage 4(9–12:00)		Stage 7(18–21:00)		Stage 9(24–27:00)		Maximal Tolerable Effort	
	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2
Oxygen uptake (ml/min per kg)	8.0	8.9	13.7	13.8	19.2	19.5	24.1	25.2	28.6	31.7
Heart rate (beats/min)	88	87	97	101	122	126	144	150	160	170
Oxygen pulse (ml/beat)	6.5	6.9	10.4	9.2	11.5	10.3	12.1	11.2	12.7	12.5
Ventilation (liters/min, BTPS)	23.1	24.4	29.6	30.9	41.4	40.7	55.5	54.5	73.5	75.7
Ventilatory equivalent ($L\dot{V}_E$/100 ml $\dot{V}O_2$, STPD)	3.29	3.39	2.54	2.80	2.54	2.67	2.69	2.69	3.03	3.15

T_1 and T_2 indicate, respectively, test results before and after training.

fects at submaximal work of the type seen in normal subjects[27] and patients after myocardial infarction.[44,45,54] Data at maximal work loads reveal higher heart rate and maximal oxygen uptake but little change in oxygen pulse, pulmonary ventilation and ventilatory equivalent.

Significance of cardiorespiratory training responses in coronary artery disease: The group trained after myocardial infarction evidenced no atypical physiologic strain in providing submaximal energy requirements. Conversely, however, patients studied after coronary artery bypass did, as denoted by increased pulmonary ventilation, ventilatory equivalent and heart rate, and lower oxygen pulse during submaximal work. Furthermore, no significant changes in submaximal work responses occurred in the four subjects who underwent coronary artery bypass surgery and trained for 12 weeks. A substantially higher heart rate at submaximal work loads than that of sedentary normal subjects is characteristic of untrained patients after myocardial infarction,[49,57,58] whereas a reduced heart rate and decreased pulmonary ventilation at submaximal work loads have been observed in patients trained after myocardial infarction.[40,45,53–55] Hence, even though the submaximal heart rate of the subjects trained after infarction was not significantly lower than that of the normal group, it should not be assumed that there was no training effect in these patients. Further evidence supporting this contention is afforded in Figure 9. The bold line represents the regression line of maximal oxygen uptake (liters/min per m^2) with age; the dashed lines represent ±1 standard deviation for 80 sedentary normal men aged 31 to 69 years[56]; the open circles indicate maximal oxygen uptake values from treadmill studies of untrained patients studied after myocardial infarction by Ord.[59] As can be seen, none of the values for these subjects fall within 1 standard deviation of the normal subjects' age-related regression line. On the other hand, the maximal oxygen uptake values of six of our subjects trained after myocardial infarction are above the line, and that of a seventh patient falls within 1 standard deviation. However, four values fall significantly below the line (more than 1 standard deviation), thus emphasizing the individual variability of maximal exercise response in patients after myocardial infarction, as noted by others.[41,47] The comparisons of group mean values for myocardial oxygen consumption in Table V lend further credence to the assumption that a significant training effect had occurred in our subjects trained after myocardial infarction.

Of the 17 patients who were not trained after coronary artery bypass surgery, the values of 9 were significantly below normal (more than 1 standard deviation) (Fig. 9). Their heart rate and pulmonary ventilation were normal, but maximal oxygen pulse was significantly decreased, which is indicative of reduced stroke volume or arteriovenous oxygen difference, or both. Their ventilatory equivalent, which reflects the amount of ventilated air necessary for utilization of 100 ml of oxygen, was significantly greater. In view of the normal ventilatory capacity evidenced, increased ventilatory equivalent could be a reflection of decreased diffusing capacity in the lungs, but more likely is a secondary indication of reduced stroke volume or decreased capacity for oxygen utilization at the muscle cell level, or both. The maximal oxygen uptake of the subjects studied after coronary artery bypass was intermediate to that recorded in previous studies for untrained and trained patients after myocardial infarction (Table V). The four subjects who trained for 12 weeks sustained a 10.8 percent increase in maximal oxygen uptake to a value comparable with that of other subjects trained after myocardial infarction. In addition, their walking time increased, as did their maximal heart rate (by 10 beats/min). Since oxygen pulse, pulmonary ventilation and ventilatory equivalent changed little, the primary mechanism for enhanced oxygen delivery at maximal effort appears to be an increased heart rate, which is uncharacteristic of trained normal subjects but has been noted previously in other subjects after myocardial infarction.[41,45]

TABLE V

Comparison of Maximal Oxygen Consumption in Untrained and Trained Postmyocardial Infarction Patients

Study	no. of Subjects	Untrained	Trained	Training Duration	Training Time/ Week (min)
Ord[59]	8	27.4*	—	—	—
Kasch & Boyer[41]	11	19.9	30.6	6 mo	210
Kasser & Bruce[49]	28	26.5†	—	—	—
Detry et al.[45]	6	27.3	32.2	3 mo	135
Present study					
Trained after infarction	11	—	32.0	6 mo to 11 yr	160
Untrained after CAB	17	28.6	—	—	—
Trained after CAB	4	28.6	31.7	12 wk	120

CAB = coronary artery bypass sugery.

* Assuming body surface area of 1.90 m^2 and body weight of 75 kg.

† Calculated from formula for estimating maximal oxygen consumption from treadmill walking time and assuming body weight of 75 kg.

The primary distinction between the exercise response of our two patient groups is that the subjects trained after myocardial infarction evidenced no differences from normal subjects at submaximal work loads and had only slight evidence of reduced maximal energy production, whereas the untrained subjects who had undergone coronary artery bypass surgery demonstrated impaired performance at both submaximal and maximal work loads, as has also been noted in other untrained patients after myocardial infarction.[49] Although the four subjects trained after coronary artery bypass had increased maximal energy production, they had no significant change in their atypical submaximal cardiorespiratory responses. The physiologic mechanisms for these findings are not really discernible without hemodynamic measurements.

Conclusions

Our data indicate the following: (1) Most subjects trained after myocardial infarction can achieve the performance levels of normal, sedentary subjects, but some do not exhibit a classic training effect, probably because of residual myocardial dysfunction. (2) Successful coronary artery bypass surgery does not entirely normalize work performance, metabolic or hemodynamic function, although angina and electrocardiographic changes can be reduced. (3) Work performance and aerobic power of patients after coronary artery bypass can be further improved by physical training, although the physiologic mechanism for these changes is not readily apparent.

Physical training improves cardiorespiratory function, which may be indicative of improved myocardial function, and aids in reducing coronary artery disease risk factors.[4,26] However, because of the relatively small number of patients studied longitudinally and the complex etiology of coronary artery disease, no conclusive evidence of less frequent recurrence rates or greater longevity has been demonstrated, although the recent report of Rechnitzer et al.[60] indicates some encouraging initial findings.

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Physical Activity After Myocardial Infarction

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Experimental and clinical research has provided substantial knowledge of the potential benefits and risks associated with the performance of physical activity by patients with uncomplicated myocardial infarction. This knowledge has resulted in the earlier mobilization, a reduction in length of hospitalization, an increase in physical working capacity and a more successful return to work of many patients. These improvements have been associated with a variety of physiologic and psychological changes produced by increased activity during each stage of the patient's recovery. During hospitalization, changes in posture and low intensity activity minimize the cardiovascular and psychological complications caused by prolonged bed rest. After hospitalization, the most valuable benefit of regularly performed exercise appears to be a reduction in myocardial oxygen demand at rest and during submaximal exertion. The unique contribution of increased physical activity to reducing the frequency and severity of reinfarction has not been adequately established but, when combined with other behavior designed to reduce risk factors, the preliminary results are favorable. For these benefits to be obtained without undue risk, exercise for the postmyocardial infarction patient needs to be individually prescribed and periodically reevaluated.

Definitive evidence is not yet available to document the unique influence of physical activity performed after myocardial infarction on subsequent cardiovascular morbidity or mortality. Numerous studies have yielded favorable preliminary or short-term results in that selected patients after acute myocardial infarction have benefited from "appropriate increases in physical activity"; they have (1) had fewer complications associated with bed rest,[1] (2) made a more successful psychological adjustment to their disease,[2] (3) shown improved cardiovascular function and physical working capacity,[3] (4) returned to gainful employment earlier and more frequently,[4] and (5) had fewer and less severe reinfarctions.[5]

Although additional research is required to determine more accurately the benefits derived by such patients from increased activity and to define how these benefits can be achieved most economically, sufficient data and experience are available to provide useful guidelines for the organization and implementation of the physical activity aspect of a cardiac rehabilitation program.[6] Recommendations for integrating increased physical activity into a total program of cardiac rehabilitation have been described previously and should include when necessary medical therapy, health education, diet modification, reduction of stress or tension, abatement of cigarette smoking, and psychological, social and vocational counseling.

The physical activity component of a comprehensive rehabilitation program should be implemented to meet the patient's specific needs during each stage of recovery. For the patient with uncomplicated

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myocardial infarction who has been admitted to the coronary care unit, a physical activity program can be organized into five rather arbitrary stages: (1) coronary care unit, (2) remainder of hospital stay, (3) a 2 to 8 week period of convalescence, (4) physical reconditioning, and (5) activity maintenance.

The activity at each stage should be systematically prescribed by a knowledgeable physician after a careful evaluation, and it should be supervised or monitored by a physician or well trained allied health personnel. The exact nature of the evaluation, supervision and monitoring will depend upon the patient's clinical and functional status. As recovery progresses, the specific activities performed and the immediate objectives of the exercise plan will change, but the general principles of exercise evaluation, prescription and training will remain the same.[7]

Coronary Care Unit Activity Program

The primary purposes of early performance of physical activity in the coronary care unit are to counter the potentially harmful deconditioning effects of prolonged bed rest and to minimize the psychological trauma of coping with the realities of surviving a myocardial infarction. In many cases the patient is unable to distinguish between a nonspecific consequence of extended inactivity and the debility directly produced by cardiac limitation resulting from the infarction. Conditions caused or aggravated by bed rest and alleviated to some extent by changes in posture and activity include decreased cardiovascular function manifested by orthostatic hypotension, venous thrombosis, reduced lung volume, atelectasis and reduced skeletal muscle tone and joint flexibility.[8]

Potential hazards of exercise: The major hazards of inappropriate exertion soon after acute myocardial infarction are considered to be the precipitation or aggravation of serious arrhythmias, congestive heart failure, aneurysm formation and cardiac rupture. However, only the hazard of an increase in premature ventricular beats during exercise by patients with coronary heart disease has been firmly documented.[9–11] There is conflicting evidence on the potential dangers of cardiac rupture or aneurysm formation with exertion immediately after infarction. The report of Jetter and White[12] that cardiac rupture occurred in 73 percent of severely psychotic patients who probably remained active during an acute myocardial infarction and died is not confirmed by recent studies of cardiac rupture occurring during sudden death in noninstitutionalized adults.[13,14] However, since in man most of the necrotic tissue resulting from the infarction is not replaced by connective tissue for about 2 weeks and complete healing requires 4 to 8 weeks,[15,16] the myocardium probably should not be subjected to major increases in heart rate or blood pressure for at least several weeks.

Animal studies: In animals, the effect of vigorous exercise soon after artificially induced myocardial infarction appears to be quite benign. Thomas and Harrison[17] found that after experimentally induced acute myocardial damage in rats severe restriction of activity increased mortality, whereas enforced vigorous exercise had no detrimental effect. Kaplinsky et al.[18] and Thompson et al.[19] were not able to reproduce the earlier findings of Sutton and Davis[20] of an increase in aneurysm formation when dogs were exercised beginning 3 days after coronary arterial ligation.

Kaplinsky et al.[18] exercised dogs vigorously for 1 hour daily for 5 weeks starting 3 days after acute myocardial infarction produced by coronary arterial ligation; these animals had no increase in size of infarction, frequency or size of aneurysms, or instances of cardiac rupture or sudden death when compared to a nonexercised control group. Similar results were obtained by Thompson et al.[19] when dogs were exercised vigorously (peak heart rates exceeding 220 beats/min) within 1 hour of total occlusion of the left anterior descending coronary artery. The results of such animal studies need to be considered with caution since they are not likely to be applicable to patients in a coronary care unit. Healthy dogs with a single artificially induced coronary occlusion without previous myocardial damage probably do not provide an acceptable model for the extrapolation of results to the diseased human heart with diffuse coronary atherosclerosis and previous myocardial necrosis.

Clinical studies: The clinical rationale for early sitting and physical activity of patients after myocardial infarction was presented in 1940 by Levine[21] and in 1944 by Dock[22] and Harrison.[23] They cautioned against unnecessary bed rest and promoted the idea of frequent postural changes for the patient and early participation in self-care activities. Their primary concerns were the complications of phlebothrombosis, embolization and congestive heart failure associated with extended bed rest and the development of "cardiac neurotics" as a result of unnecessary and prolonged restriction. In the 1950's the concept of the "armchair" treatment was promoted by Levine.[24]

Levine and Lown[25] demonstrated that cardiac output was reduced by 23 percent when patients who had had a myocardial infarction changed from a supine position to sitting in a chair. Coe[26] found the mean cardiac work in such patients to be 23 percent less while sitting than while reclining. More recently, DeBusk et al.[27] demonstrated that changes in posture or selected passive and active exercises can be performed by patients in the coronary care unit without significant increases in work of the heart (blood pressure-pulse rate product) or ventricular arrhythmias. Fareeduddin and Abelmann[28] have demonstrated that the impaired orthostatic tolerance produced by complete bed rest in many patients after infarction is preventable or reversible by early ambulation or modified bed rest allowing passive movements and occasional sitting.

Activity program in the coronary care unit: For the patient with the uncomplicated myocardial infarction (no evidence of shock, heart failure, intractable angina, or uncontrolled arrhythmia) low level passive and active isotonic activities normally can be

initiated in the coronary care unit. These activities should be carried out under the direction of the patient's physician or the medical director of the coronary care unit, or both. Acceptable activities and techniques for their instruction and supervision have been described in detail.[6,27,29] Usually included at this time are self-care activities (self-feeding, washing of face and hands, shaving, use of bedside commode with assistance), active and passive movements of arms and legs while in bed and changes in posture to include sitting on the side of bed with feet supported or in a chair. All of these activities should be supervised by a well trained nurse or therapist with continuous electrocardiographic monitoring and periodic evaluations of blood pressure and symptoms.

Indications of an inappropriate increase in exertion during the coronary care unit activity phase include (1) unexpected fatigue, weakness or dyspnea, (2) development of or increase in angina, (3) significant rhythm or conduction disturbances, (4) increased ischemic-type S-T segment displacement, and (5) increase in heart rate by more than 20 beats/min over the resting rate or a decrease by more than 10 beats, and (6) a persistent decrease or substantial increase in systolic blood pressure. If any of these responses occur during activity, bed rest should be resumed until the patient's status is evaluated and a revised activity plan developed.

Activity During Remainder of Hospital Stay

Upon transfer from the coronary care unit and in the absence of cardiovascular complications the patient should continue a planned program of individually prescribed activity. The major objectives of physical activity during this stage are to continue to prevent the harmful physiologic and psychological effects of prolonged bed rest, reduce the duration of hospitalization and increase cardiovascular functional capacity to a level that will allow a reasonable degree of self-care after discharge and a more rapid return to work.

Mobilization of patients after discharge from the coronary care unit and the effects of a shortened hospital stay have been evaluated by several groups.[30–32] In general these studies have demonstrated that there are no adverse clinical effects from early mobilization in selected patients after myocardial infarction and that there may be some benefit by the reduction of physiologic and psychological complications and an earlier or more frequent return to work. The rationale for and success rate of early mobilization and discharge after myocardial infarction were recently reviewed by Rose.[33]

Activity program: Appropriate activities during this phase of recovery include longer periods of sitting in a chair, increased self-care activities, rhythmic exercises using arms, legs and trunk, and slow ambulation in the hospital room and later in the corridors. For patients who progress rapidly, limited stair climbing might be permitted during the latter portion of this phase.[34]

Increases in exertion should be performed by the patient at least several times a day unless contraindicated by signs or symptoms. Each activity session should have alternating periods of exercise and rest. These sessions should not be conducted immediately after meals and can be supplemented by calisthenics performed while in bed. Unnecessary isometric exercises, particularly in conjunction with a Valsalva maneuver, should be avoided. During and after each new activity the patient should be evaluated for changes in electrocardiogram, blood pressure and heart sounds.

During the latter stages of hospitalization, instructions should be provided to the patient and his family about particular activities to be performed or avoided after leaving the hospital. Topics that need to be covered include sexual activity, use of stairs, lifting and carrying of relatively heavy objects and activities in hot, cold or humid environments.

Testing of functional capacity: One means of improving the appropriateness of the recommendations on physical activity to the patient going home is to carefully evaluate his symptom-free functional capacity while he is still in the hospital. This can be achieved by monitoring the electrocardiogram, heart sounds, blood pressure and symptoms during ambulation in the corridor or during stair climbing. Low level multistage exercise testing using either a stationary bicycle ergometer or treadmill as soon as 3 weeks after infarction has been demonstrated to be safe and can provide useful prognostic information as well as objective criteria for exercise prescription.[35]

Activity Program During Convalescence

The primary goals of an activity regimen during this phase of recovery are (1) to increase gradually the frequency, duration and intensity of activity so that by the 8th to the 12th week after infarction the patient with an uncomplicated infarction has achieved a level of exertion commensurate with that required by the job to which he is scheduled to return, and (2) to provide psychological support to the patient and family for the prospect of successful long-term recovery. If return to work is not a consideration or if the job requires a peak energy expenditure greater than 6 to 8 METS (multiples of resting oxygen consumption) then the activity level during this time should reach that necessary for complete self-care and the safe performance of selected leisure time activities, including limited sexual activity.

An objective evaluation of the effects of increased activity between the 4th and 12th weeks after infarction has been reported by Brock.[36] As a result of an 8 week exercise program (1 hour, three times a week) his patients had a small reduction in pulse rate at the same work load and a large (60 to 70 percent) increase in physical working capacity and peak oxygen consumption. The increases in working capacity and oxygen consumption are difficult to interpret because of a change in the criteria for terminating the exercise test from a pulse rate of 65 percent of the age-

TABLE I

Indexes of Myocardial Oxygen Demand Before and After Physical Conditioning in Male Patients with Cornary Heart Disease

Study	Patients (no.)	Age (yr)	Index	Rest		Exercise		Exercise Intensity
				Before	After	Before	After	
Redwood et al.[43]	7	48	Triple product	...	...	4300	3521	Same submaximal workload
						4300	4885	At onset of angina
Frick & Katila[41]	7	47	Tension-time index	2519	2941	5168	4382	Same submaximal workload
			Double product	103	107	262	242	Same submaximal workload
Clausen et al.[42]	9	52	Tension-time index	2470	2380	3943	3393	Same submaximal workload
			Double product	...	...	204	166	Same submaximal workload
Hellerstein[40]	100	49	Double product	...	...	248	193	Same submaximal workload
Detry et al.[39]	12	49	Double product	81	64	116	94	45% of pretraining $\dot{V}O_2$ max
						166	137	75% of pretraining $\dot{V}O_2$ max
Kasch & Boyer[44]	11	50	Double product	106	85	163	156	286 kg-m before; 382 kg-m after
						247	296	Maximal workload

Double product = [heart rate (beats/min) × systolic arterial pressure (mm Hg)]/100; kg-m = kilogram-meters of work per minute; tension-time index = area under systolic brachial arterial pressure curve × heart rate (mm Hg sec/min); triple product = heart rate (beats/min) × systolic arterial pressure (mm Hg) × ejection time (seconds); $\dot{V}O_2$ max = maximal oxygen consumption.

adjusted maximum before training to a pulse rate of 75 to 80 percent after training. How much of the improvement in physical working capacity during convalescence is due to the natural recovery from the infarction and bed rest and how much is due to the conditioning program has not been established.

Activity program: Most usual light household and self-care activities can be permitted except floor scrubbing, hand washing and hanging of clothes, bed making and similar activities requiring prolonged or vigorous effort with the arms and shoulders. Again, isometric exercises using the arms, such as those required in carrying heavy objects like a suitcase, need to be avoided. Jackson et al.[37] have demonstrated that this type of activity can create a disproportionate work load on the myocardium in relation to total body energy expenditure.

The patient who remains asymptomatic should gradually increase his level of activity at his own pace so that by the end of the 4th or 5th week after infarction he can walk a total of 1/2 to 1 mile a day comfortably. These walks should be divided into two or three periods of approximately equal duration. The program should remain within each patient's capabilities and he should remain symptom-free.

Before increasing the pace and distance of exercise further in the 6th through 8th weeks after infarction, the patient should be carefully reevaluated by his physician. This assessment should include a medical history, with careful questioning about the level of daily activity the patient has reached and his symptomatic response to this activity, physical examination, and appropriate laboratory tests including a resting electrocardiogram.

Functional assessment: Cardiac function should be assessed by a multistage exercise test in which the highest work load performed is greater than that of the activities performed by the patient during the previous week, such as walking half a mile or stair climbing. The response to this effort test can serve as a valuable guide to the physician in regulating the patient's future activities. Adverse responses to the exercise test, which indicate a need to decrease rather than increase activities, include a disproportionately rapid and large rise in heart rate or blood pressure, a sustained reduction in systolic blood pressure of more than 10 mm Hg, significant changes in the electrocardiogram, increasing angina, or a decrease in working capacity.

The patient with an improved exercise test response should be advised to increase the duration and speed of walking during the next several weeks in order to increase his endurance and strength in preparation for his return to work. In general, in the patient who has shown no adverse response to the preceding carefully monitored graduated activity program, a reasonable goal is to obtain a capacity for walking a mile in 20 to 25 minutes at least once a day, with a peak level of energy expenditure not exceeding 4 to 5 METS. The principles of exercise prescription for coronary heart disease patients have been presented in detail by Hellerstein and co-workers.[38]

Physical Conditioning

Many patients without clinical complications 8 to 24 weeks after infarction become candidates for a program of higher intensity physical activity. The major objectives of such a physical conditioning program are to (1) improve physical working capacity, (2) decrease symptoms and signs of ischemic heart disease at rest and during exertion, (3) increase speed and frequency of return to gainful employment, and (4) reduce the chances of reinfarction or sudden death. Whether or not these changes take place appears to be dependent upon a combination of hemodynamic, metabolic and psychological alterations.

Hemodynamic and Metabolic Changes

In many respects the hemodynamic and metabolic changes that occur in cardiac patients with conditioning are quite similar to the changes seen in their age-matched asymptomatic, sedentary counterparts except that the magnitude of change is usually less and the interindividual variability is substantially greater for the former.[3] Some factors contributing to this variation in conditioning response include age, degree of myocardial necrosis and ischemia, interval after infarction, cardiovascular functional capacity at the start of training and the magnitude of the conditioning stimulus (intensity, duration and frequency). Also, the load (resting, submaximal or maximal) and body position (lying, sitting or standing) at which hemodynamic measurements are determined influence the nature and magnitude of measurable changes.

Improvement produced by physical conditioning in the working capacity and clinical manifestation of many patients after infarction results from a reduction in the discrepancy between myocardial oxygen supply and demand due primarily to a decrease in demand. A reduced myocardial oxygen demand at rest and submaximal exercise is reflected by a significant reduction in such indexes of myocardial oxygen requirement as pressure-rate product,[39,40] tension-time index[41,42] and the triple product[43] (heart rate [beats/min] × systolic arterial pressure [mm Hg] × ejection time [seconds]) (Table I). Major changes contributing to the lowering of these indexes are bradycardia and a decrease in systemic arterial pressure.[44] The bradycardia is usually associated with a small increase in both stroke volume and arteriovenous oxygen (a–v O_2) difference[45] resulting from increases in skeletal muscle mitochondria size and number with augmented levels of activity by the mitochondrial respiratory enzymes.[46]

Increases in physical working capacity and aerobic capacity in patients not limited by manifestation of ischemic heart disease before conditioning have been reported.[39,43,44,47] Whether these changes result from an expanded a–v O_2 difference, a greater stroke volume or a combination of both as seen in healthy young adults has not been measured.[3] Extrapolations from hemodynamic measurements made during submaximal exercise indicate that increases in either a–v O_2 difference[39] or stroke volume[42] may be the major contributor to this enhanced capacity. Patients with substantial myocardial damage or ischemia resulting in poor left ventricular compliance probably are extremely limited in their ability to increase stroke volume with physical conditioning.

Changes in coronary circulation: Studies using coronary arteriography do not support the hypothesis that physical conditioning contributes significantly to coronary artery collateralization in patients with coronary artery disease as observed in some animal studies.[48,49] Ferguson et al.[50] studied 14 patients with significant obstructions in one (6 patients) or two (8 patients) coronary arteries who exercised three times a week for 13 months. The average increase in maximal oxygen consumption was 25 percent (21.9 ± 4.8 to 27.4 ± 4.1 ml/kg per min) but only two patients with progressing obstructions manifested new collateral vessels. Similar results were observed by Conner and La Camera[51] in patients who underwent 6 months of physical conditioning after myocardial infarction.

Redwood et al.[43] found that as a result of physical conditioning the level of the triple product at which angina occurred was increased in some patients, possibly as a result of increased myocardial oxygen supply. Similar results using S–T segment displacement as a measure of ischemia have been reported by Kasch and Boyer,[44] but Detry and Bruce[47] found no significant decrease in S–T segment depression at the same double product. Such changes could result from a reduced myocardial oxygen requirement due to a more synchronous contraction and smaller heart volume during exertion or a slight increase in myocardial oxygen extraction without any increase in coronary blood flow.

Other alterations possibly resulting from physical conditioning activities but not well defined in patients who have had a myocardial infarction include decreases in serum lipoproteins, especially triglycerides,[52] a reduction in plasma insulin,[53] enhancement of blood coagulation and fibrinolytic activity[54] and decreases in plasma catecholamine levels.[55] If some of these changes do occur they could reduce the patient's risk of reinfarction or sudden death.

Some of the improvements seen in the physical working capacity and physiologic responses to exercise by patients after myocardial infarction may be the result of psychological changes associated with their participation in a physical conditioning program. Both objective and subjective measures indicate that, for many such patients, physical conditioning results in a reduction in depression and hypochondriasis, an increase in self-confidence, particularly as it relates to the performance of physical tasks, and an improved sense of well-being.[40,56] In general, the magnitude of psychological improvement appears to be related to the degree of neurosis or anxiety upon entrance into the program and may be due more to the attention received during supervised exercise programs than to the effects of the activity itself.[2]

Recurring Myocardial Infarction and Mortality

The influence of physical conditioning on the frequency and severity of recurring myocardial infarction has not been adequately defined using random allocation of a sufficiently large number of patients into exercise and control groups. Table II contains a comparison of the mortality rates reported for patients who participated in a program of active rehabilitation after infarction and patients with similar characteristics who did not participate in any structured program. A consistently more favorable mortality rate is shown for the rehabilitation program participants; however, there are serious questions as to the comparability of the active and nonactive groups in each study regarding the severity of illness and the likelihood of reinfarction. Also, other coronary heart disease risk factors were not well controlled and sometimes intentionally altered as a part of the rehabilitation program.

The only reported study using a randomized control design in which reinfarction and mortality rates were analyzed showed no differences between supervised exercise program participants and control subjects.[61] Of 298 consecutive male patients under age 65 who were treated in the University Central Hospital, Helsinki in 1969 with a diagnosis of acute myocardial infarction, 158 met the criteria 6 to 8 weeks after hospital admission for a study of supervised physical activity. On the basis of their year of birth, the patients were randomly assigned during their hospital stay into control (odd year) and training (even year) groups. Control group participants received regular medical care; the training group members were requested to participate in a supervised exercise program approximately 1 hour three times a week during the first five months and then twice a week from the 5th to 12th months. During the first 20 months after initiation of the training program, of the 81 control patients 4 had a nonfatal reinfarction and 7 died from reinfarction; of the 77 training group patients, 6 had a nonfatal reinfarction and 8 died from reinfarctions. These differences were not statistically significant. A major limitation of this study was the poor adherence by the training group patients to the supervised exercise program.

Return to gainful employment: Whether physical conditioning increases the speed and frequency at which patients who have had a myocardial infarction return to gainful employment has not been satisfactorily determined. Kentala[61] found no difference in his exercise and randomly allocated control groups, whereas Kellerman et al.[62] observed an increase in frequency of return to work among rehabilitation program participants. For economic reasons, a definitive answer to this question needs to be determined but will be extremely difficult to obtain because the number of patients returning to work after a myocardial infarction depends, to a large extent, on factors other than their clinical status or physical working capacity.[63]

TABLE II

Deaths Due to Myocardial Infarction in Rehabilitation Program: Participants and Nonparticipants

Study	Death Rate Due to Recurrent Myocardial Infarction (no. per 100 man years experience)	
	Rehabilitation Program Participants	Comparison Group
Hellerstein[40]	1.95	4.5–6.0*
Gottheiner[57]	3.6	12.0
Brunner[58]	3.1	10.8
Rechnitzer et al.[5]	3.5	6.8 (matched control group)
Kellerman[59]	0.8 (long-term group)	2.5
Bruce[60]		
	Cardiovascular Death Rate	
	Observed	Expected†
	3.1%	11.2%

* Usual mortality rate of comparable coronary subjects treated in traditional manner as stated by author.

† Based on follow-up experience of 180 patients with myocardial infarction admitted to four local hospitals and discharged alive.

Supervised Conditioning Programs

Because patients who have had a myocardial infarction are at increased risk of exertion-induced cardiac arrest, it is generally recommended that their participation in physical conditioning programs be supervised by a knowledgeable exercise leader and physician or nurse trained and authorized to perform cardiopulmonary resuscitation.[60] How long patients should be under medical supervision while performing relatively high level exercise has not been established. Many cardiac rehabilitation programs in the United States graduate patients to nonsupervised conditioning exercise programs 1 year after infarction; others suggest supervision on an indefinite basis for safety reasons.[60]

A second reason for encouraging supervised programs is the reasonably frequent experience that patients who attend supervised exercise sessions after infarction tend to stop exercising if they are provided an exercise program to perform on their own.[59,64] To determine which patients should have supervision for how long, it is necessary to be able to select accurately those patients who are at very low risk of cardiac arrest or myocardial infarction produced or aggravated by exertion. Those patients at low risk can be encouraged to exercise on their own using an individualized exercise prescription based on and revised periodically according to the results of a medical reevaluation. Because of advanced age, cardiovascular complications or other health problems, certain patients cannot increase their level of exertion above that

achieved during the convalescent stage and should be discouraged from doing so.[65] The inability of patients with a low physical working capacity to increase their capacity after 6 months of regular participation in a conditioning program is considered an indication for reevaluation and possibly alternative therapy.[34]

Conditioning program activities usually include walking, jogging, running, stationary bicycling, swimming, calisthenics and selected games. The intensity, duration and frequency of activity should be prescribed on an individualized basis. Intensity for these types of activities can be at 60 to 85 percent of the patient's physical working capacity as measured by a multilevel exercise test.[38] Recommended duration is 30 to 60 minutes at a frequency of three to five times a week.

During the early phases of physical conditioning, exercise bradycardia occurs only when trained skeletal muscles are used. For example, Clausen et al.[66] trained two groups of men using a bicycle ergometer; one group used their arms while the other used their legs. When tested with arm and leg cycling after training, the men had a lower heart rate only when using the trained limbs. Thus, if one of the objectives of the conditioning program is to improve physical working capacity for a task that requires arm work, then activities using the arms should be included. If arm exercises are used it is important to remember that the double product is higher for arm work than for leg work having the same total body oxygen requirement. Also, because of the low arm strength of many adults it is important to keep the resistance level in arm exercises low in order to avoid the rapid increase in myocardial oxygen demand resulting from a pressure response produced by isometric or heavy resistance activity.[37]

Maintenance Activity Program

Once a desirable cardiovascular functional capacity has been achieved, a long-term program of exercise maintenance should be considered. The goal of this program should be to provide the patient with a level of activity that will maintain his cardiovascular functional capacity and efficiency, assist in maintaining optimal body weight and help him to retain a physical working capacity commensurate with his occupational needs and leisure time interests.

A critical factor in the design of a maintenance program is the decision as to whether it should be performed only with medical supervision. Sufficient follow-up data are not available to determine the susceptibility of a particular patient to cardiac arrest or reinfarction precipitated by an increase in physical activity. In an attempt to make such a decision, all pertinent clinical and laboratory data on the patient should be considered with emphasis placed upon a recent near-maximal or maximal multilevel exercise test. Performance at a level of 10 to 12 METS without symptoms or adverse effects would indicate that at least for the present time activity such as jogging, moderate running, hiking, swimming, doubles tennis, badminton and most gardening are within the patient's capacity. Additional information about the acceptability of a particular activity can be provided by ambulatory electrocardiographic monitoring. This might be particularly useful if the activity includes intermittent exercise loads, heavy use of the arms, and psychological stress such as that possibly associated with competitive sports or anxiety-producing work situations, or major changes in environmental conditions (temperature, humidity or altitude).

The maintenance plan should include a variety of activities that can be performed well within the patient's functional capacity, are of interest to him, and are primarily aerobic but still of sufficient duration and intensity to maintain an "appropriate functional capacity."

Conclusions

By proper patient selection, exercise prescription, program supervision and periodic reevaluation, patients recovering from an acute myocardial infarction can safely perform increasing levels of physical activity. Substantiated benefits derived from increased activity include fewer complications due to bed rest and an increased symptom-free working capacity as a result of improvement in hemodynamic and metabolic function. As a part of a comprehensive cardiac rehabilitation program, physical activity aids in reducing psychological maladjustment and improves success of return to gainful employment. Definitive evidence as to the benefit of increased activity on future cardiovascular morbidity or mortality of patients with coronary heart disease requires a multicenter, cooperative secondary prevention trial. Concurrently with such a major research project, present knowledge of the benefits derived from effectively operated cardiac rehabilitation programs justifies the expansion of these services and increased third-party payment for medically operated programs.

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Coronary Heart Disease as a Pediatric Problem

Prevention Through Behavior Modification

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Risk factors for coronary heart disease may be present in early childhood. Primary prevention of coronary atherosclerosis requires early identification and vigorous management of risk factors, and the pediatrician and family physician have a major role in this approach. Alteration of behavior with emphasis on exercise of the endurance type and more rational dietary habits are advocated. The beneficial effects of exercise may occur without alteration of coronary risk factors. Early institution of educational programs and constructive physical activity has the potential to influence favorably cardiovascular health at an early stage.

Predictive and preventive cardiovascular medicine should begin early in life. Current emphasis on this approach is based on recent appreciation of the early appearance of coronary risk factors in the pediatric age group and the potential for their alteration by systematic evaluation and management.[1] Most of these risk factors, such as hyperlipidemia, hypertension, cigarette smoking, obesity and physical inactivity, have been attributed to a combination of genetic and environmental influences[2] and, to the extent that the latter effect is operative, these factors are amenable to modification. Recent epidemiologic studies have demonstrated a considerable prevalence of indicators of high coronary risk in children in the teen and preteen years. These have included elevated serum levels of cholesterol and triglycerides,[3–5] obesity,[5–8] hypertension[5,8] and inadequate exercise capacity.[5]

The magnitude and early onset of the problem are exemplified by recent data. Thus, in one study of 95 boys aged 8 to 12 years, 63 percent of the group had one or more coronary risk factors and 17 percent had two or more risk factors.[5] Serum cholesterol was greater than 200 mg/100 ml and triglycerides were greater than 100 mg/100 ml in 20 percent and 8 percent, respectively, of the subjects; 13 percent of the group demonstrated obesity (greater than 25 percent body fat). In another study of more than 4,800 school children 6 to 18 years old, serum cholesterol was greater than 220 mg/100 ml in 5 percent, blood pressure exceeded 140/90 mm Hg in 2 percent of those older than 9 years and 12 percent were obese.[8]

Although applicability of adult coronary risk factors as predictive indexes in children has not been substantiated by long-term studies, the extent of the current coronary epidemic and its potential for mitigation by early intervention have resulted in major interest in the pediatric aspects of management. This approach to early reduction and prevention of known coronary risk coronary factors in childhood constitutes primary prevention.

Primary Prevention

Primary prevention of those influences associated with atherosclerosis should be a principal goal of the pediatrician and family physician. Applying this concept may entail a fundamental reorganization

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of pediatric care, permitting certain aspects of treatment of routine upper respiratory and gastrointestinal problems and performance of standard immunizations and regular physical examinations to be handled by paramedical personnel, such as the pediatric nurse-practitioner, so that the pediatrician's time can be spent more beneficially in preventive medicine. The expertise of the physician should be directed to detection of the risk factors that predispose to premature atherosclerosis. In addition, his time and effort should be spent in counseling the family, particularly the mother, in early modification of life style patterns.

Through such efforts by the pediatrician and family physician, the initial formation of constructive patterns for early modification of factors associated with high coronary risk during childhood may be accomplished. In addition to detection of risk factors in children, these findings can also lead to recognition of occult or clinical disease in other members of the family. The child therefore becomes a source of case finding for other members of the family. The role of the physician who treats children or the entire family unit is a vital one for rearing upcoming generations with new and better health habits.

Role of Exercise

Exercise has recently gained interest as part of a multifaceted intervention program aimed at improving cardiovascular hygiene. Although systematic physical conditioning involving exercise of the endurance type has been considered beneficial to the cardiovascular system, the precise mechanism of such an effect has not been completely clarified.[9] Evaluation of the influence of exercise on the coronary risk factors per se has been difficult. The investigator who undertakes to evaluate the role of physical fitness in altering risk factors often finds that his subjects spontaneously change their habits of smoking, recreation, sleep and other routines that singly or together affect the risk factors as a whole. It is therefore difficult to separate the direct effect of the exercise program from the commonly associated subtle changes in living patterns.

Our studies[10] reveal relatively small effects of exercise training on coronary risk factors. For example, although measurements of skin fold thickness indicating a decrease in fat and an increase in lean body mass, serum cholesterol decreases only 3 to 5 percent and diastolic blood pressure is reduced only 6 to 8 percent. Alteration of risk factors by exercise in other studies[9,11] also indicates that even when these changes are statistically significant, their magnitude is modest. In addition to lack of data indicating that exercise has a major effect on known coronary risk factors, there is no firm evidence that it alters atherogenesis or enhances the coronary collateral circulation. However, it has been suggested that augmented diameter of the vessels of the native coronary circulation may result from exercise.[9] Atherosclerosis would thus be less consequential and its effects delayed.

The beneficial effects of exercise in patients with ischemic heart disease, for example, decreased angina pectoris and increased functional capacity, appear to be closely related to major alterations in the cardiocirculatory response to exercise of the endurance type. Thus, the trained state is associated with a reduced heart rate and, commonly, a reduced blood pressure at any given level of exercise.[12] Increased oxygen extraction and other metabolic adaptations by skeletal muscle are associated phenomena[13] that allow similar external performance at a reduced level of cardiac activity. The result is decreased mechanical effort of the heart and thereby reduced myocardial oxygen consumption.[14]

Thus, exercise may exert important effects on the cardiovascular system independent of any influence on coronary risk factors. It is suggested that exercise may be operative in coronary heart disease by (1) decreasing the clinical manifestations of atherosclerosis in the young, and (2) enhancing individual adaptation to atherosclerosis once the disease is clinically established.[15]

New Approaches to Exercise Programs

If it is accepted that early control of hypertension and adoption of attitudes and behavior leading to altered diet, nonsmoking and avoidance of a time-oriented competitive stress pattern are important in the prevention of premature atherosclerosis beginning early in life,[16] then we should also alter exercise patterns and physical activity habits in children to achieve the most beneficial cardiovascular effects. Activity programs for children should emphasize cardiovascular endurance fitness rather than the conventional athletic games, which are contests of skill and agility and have little positive effect on the cardiovascular system. Activities that children can learn and continue throughout life such as hiking, walking, swimming, jogging, cycling, rowing, folk dancing, square dancing and other activities of the continuing endurance type should be fostered. It is important to recognize that competitive sports do not necessarily produce physical fitness and that children as well as adults should be physically fit first before engaging in sports.

Physical activity appears to be protective only when it operates above a certain threshold level, that is, a level at least 70 to 75 percent of a person's work capacity.[9] Thus, we need new games that are continual and rhythmic and enjoyable and also require enough work to increase cardiovascular endurance. These activities should begin early in the school years, certainly by the first grade. Most elementary schoolyard games are largely passive with short bursts of activity. Activity that is vigorous and imaginative with running, jumping and climbing would be more constructive. Rhythmic, continual group exercises to music and group gymnastics can also be utilized. Schoolyards need jumping pits, horizontal ladders, obstacle courses, balance beams, large ropes to swing on and large areas for running. Changes are re-

quired in the usual sterile playground consisting of some swings, a softball area and a jungle gym. These should be replaced with innovative, interesting and challenging types of programs and equipment that can contribute to the development of the cardiovascular system in a protective way. Competitive sports should be deemphasized and lifelong physical activity emphasized.

New concepts of recreation demanding less participation of the spectator type and more active involvement are required. We need to encourage and provide facilities for family cycling, hiking, skiing, water activities and winter recreation. In other words, family fitness should become a way of life.

Education

How can these changes be brought about? 1. Education is of prime importance. Not only should there be an emphasis on health education in the schools but public education through the media and community groups is necessary in a consistent effort to effect desirable changes for all ages.

2. There is a need for a new image of health and for new health education. The past emphasis has been primarily on knowledge concerning health problems in the belief that such knowledge will affect behavior. It is now apparent that at least equal attention must be given to influencing attitudes and behavior. It is time to stop discussing data in our school and community programs and to focus on changing behavior. This approach, known as behavior modification,[17] is based on principles of learning. It assumes that if a maladaptive behavior is learned, it can be retrained or replaced with a more adaptive one. Even if a behavior is originally determined by genetic or physiologic factors, it can be altered and shaped to be adaptive.

3. There is a need for comprehensive school health education beginning at the elementary level. The health education programs in secondary schools reach children too late. Proper health habits must begin long before the high school level. Most school health education at the elementary level lacks professional leadership and is largely ineffective. Enlightened physicians must play an active role in directing health education in the schools.

4. The most important need is for physicians to become more actively engaged in preventive programs. Physicians should be leaders in primary prevention. Some of the energy and resources of medicine now directed toward the treatment of the disease itself must be aimed at primary prevention.

5. Trained paramedical personnel should be developed to aid the physician in promoting fitness and healthful behavior patterns.

The potential benefits of a comprehensive program directed toward improving cardiovascular health are indeed monumental. The lack of significant, associated disadvantages further emphasizes its rationale and virtue.

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Physical Fitness Programs for Adults

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The sedentary habits, occupational stresses and high caloric intake of adults have spurred an interest in physical exercise. Participation in some form of physical activity is necessary to maintain acceptable levels of muscular strength, range of motion of the joints, and endurance. Ideally, each person over the age of 35 years should have a progressive exercise test administered by a physician before undertaking an exercise program. An exercise prescription must take into account the type of activity, intensity of training, frequency of participation and duration of each exercise session. Both an understanding of exercise physiology and a knowledge of exercise programs are essential to sound patient counseling and management.

In a recent national physical fitness survey conducted for the President's Council on Physical Fitness and Sports,[1] 3,875 men and women over the age of 22 years were interviewed. The results indicated that 55 percent of adult Americans, 60 million persons, engage in some form of exercise. Of these 60 million it is estimated that 44 million walk, 18 million bicycle, 14 million swim, 14 million do some type of calisthenics and 6.5 million jog. Many active adults participate in more than one form of exercise.

Although more than half of adult Americans engage in some physical activity, many are not physically educated. They must be helped to make intelligent decisions on the selection of physical activities. And they must be informed about the importance of the frequency of participation, the duration of activity sessions, as well as the intensity of the energy expenditure during exercise. Frequency, duration and intensity and type of exercise are the key words in fitness programs for adults.

Research has provided the scientific basis for exercise decisions: frequency, duration and intensity. It is a matter of time before this information is translated and written in meaningful terms for the general public. In the meantime the American adult relies on the guidance of physicians and physical educators and directors. All too often he does not seek counsel. He relies on past experience and initiates an exercise program on his own. The activity he selects and the intensity of his effort may result in unnecessary pain and discomfort. Sometimes sudden death occurs. This is a high price to pay for an honest attempt to achieve physical fitness.

Programs of physical fitness are available to the public through government publications and the popular press. The books and pamphlets are attractively presented and read by millions of Americans. Each publication has its own special way of convincing adults to do something about the "middle-age troika": weak musculature (especially of the abdomen), lack of flexibility and low endurance capability. The reader has his choice among programs whose requirements range from a few minutes of daily activity to 60 minutes of exercise a day, 6 days a week. Fortunately, each publication also recommends

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TABLE I

$\dot{V}O_2$max Relative to Age for Moderately Active Men

Age (yr)	$\dot{V}O_2$max (ml/kg per min)	Age (yr)	$\dot{V}O_2$max (ml/kg per min)	Age (yr)	$\dot{V}O_2$max (ml/kg per min)	Age (yr)	$\dot{V}O_2$max (ml/kg per min)
20	52.8	30	48.4	40	44.0	50	39.6
21	52.4	31	48.0	41	43.6	51	39.2
22	51.9	32	47.5	42	43.1	52	38.7
23	51.5	33	47.1	43	42.7	53	38.3
24	51.0	34	46.6	44	42.2	54	37.8
25	50.6	35	46.2	45	41.8	55	37.4
26	50.2	36	45.8	46	41.4	56	37.0
27	49.7	37	45.3	47	40.9	57	36.5
28	49.3	38	44.9	48	40.5	58	36.1
29	48.8	39	44.4	49	40.0	59	35.6

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that the reader consult his personal physician before beginning an exercise program. Accordingly, the intent of this paper is to provide the physician with an understanding of the principles of exercise programs that will enable him to provide intelligent counsel to his patient.

Motivation

Adults decide to exercise for a variety of reasons—health, recreation or relaxation, opportunities for social contact or factors related to personal image and self-esteem. Many Americans believe that exercise is "good for you" and, if performed regularly, will confer health benefits. Some believe that exercise controls body weight. Others maintain that exercise strikes the balance between work and play or serves as a vehicle to ameliorate tensions and frustrations. Man is a social being. Exercise programs, sport and games present an opportunity to meet others with similar interests. A reason for exercise may be to achieve a feeling of euphoria, a feeling that is difficult to quantify or explain. All of these reasons are valid and have one thing in common: They are endogenous. The final and conclusive reason for exercise is the physician's recommendation that if the patient doesn't begin to change his life style and become physically active he may soon have serious medical problems. A previously sedentary adult will benefit from an exercise program if he is motivated. Exercise leaders and physicians must allow for differences in attitude toward exercise and prescribe programs that meet individual needs. A man's adherence to an exercise program depends almost entirely on his motivation.

Scientific Evaluations

Table I, developed by Hodgson,[10] presents data on maximal oxygen uptake ($\dot{V}O_2$ max) for moderately active men aged 20 to 59 years. The equation ($\dot{V}O_2$ max, ml/kg per min = 61.6 − 0.44 Age) used to construct Table I was developed from mean values reported in nine studies with a total of 302 men plus data from lumberjacks referred to by Andersen.[11] Like these moderately active men, sedentary men, after a period of conditioning, showed a similar reduction in $\dot{V}O_2$ max with age, but their data were not included. In these studies, moderately active was defined to include men who were former athletes or were active by occupation or recreation. Table I provides the physician with objective data against which he can measure his patient's capabilities. A reliable assessment of performance capability is a critical aspect of an exercise prescription. A laboratory assessment of aerobic capacity provides the physician with the objective criteria needed for diagnosis and recommendation.

Types of Programs

It has been well established that there is a high degree of specificity in physical fitness programs. Fitness programs can be designed for specific goals. If the desired goal of the exercise program is muscular strength, strength-producing types of activities (dynamic weight training; static isometric exercise) will result in higher levels of strength during performance. If increased range of motion of the joints is the desired goal, exercise programs can be designed to increase a subject's flexibility. If cardiorespiratory endurance is the goal, programs of aerobic training that include a wide variety of human movements will result in increased endurance capability. Many agency-sponsored programs (Jewish Community Centers, Young Men's Christian Association) attempt to incorporate all three goals in an exercise session: strength, flexibility and endurance. Published programs for the general public may emphasize the importance of only one factor. All three factors are important, but priority and emphasis should be placed on the cardiorespiratory organs. Aging man needs a frequent training stimulus to the heart and circulatory system.

Ideally a physical fitness training session should consist of a warm-up period, an endurance phase, a game (optional) and a cooling down period.

Warm-up (3 to 5 minutes): The warm-up period is recommended to prepare the body for sustained activity. A warm-up period increases blood flow and stretches postural muscles. It is a period of adaptation. Rhythmic movements of the segments and

trunk are precautions against the occurrence of skeletal muscle strain.

Endurance (15 to 30 minutes): The training of the oxygen transport system is essential. The cardiopulmonary system should be stressed by activities of graduated intensity. The intensity of work loads is changed when adaptation occurs. Table II lists some typical activities that improve endurance of performance.

Games, fun (10 to 15 minutes): A game is defined as any competition in which the object is to gain a temporary advantage over one's opponent. In prophylactic exercise programs the games portion has a single goal—fun. Participation in games should be physical self-expression for its own sake. Winning or losing should be secondary to play. Men who are symptomatic or at risk of coronary disease need creative outlets for their energy expenditure. The need to win or to be first is often the reason why a man becomes an early candidate for myocardial infarction. Games with few rules and many participants are ideally suited for a structured or group exercise program.

Cooling down (3 to 5 minutes): At the completion of an exercise session some time should be devoted to the cooling down process. Exercise raises core temperature and increases heart rate and arterial pressures. The last few minutes of exercise should include gross body movements. The intensity of these movements should be gradually decreased. Activities that maintain or improve range of motion of the joints are desirable.

Exercise Studies of Middle-Aged Men

Since 1964, nineteen studies have been published on the effect of physical training on maximal aerobic power.[12–27] These studies ranged from 5 weeks to 2 years in duration; the subjects, all male, ranged in age from 20 to 60 years and exercised 2 to 6 days a week. All 19 studies reported increases in maximal oxygen uptake between the initial and final testing sessions. A 6 percent increase was reported by Wilmore et al.[23]; Cureton and Phillips[27] reported an increase of 38 percent. Thirteen of the 19 studies reported increases in aerobic power in excess of 15 percent of the base-line measures.

The subjects of these studies participated in a variety of aerobic training activities including calisthenics, jogging, running, walking, bench-stepping, bicycling and swimming. Some programs included games of handball, paddleball or volleyball. The results indicate that aerobic power increases with training and that this training effect occurs at all age levels. The degree of improvement depends upon the type of activity, the frequency of training and the intensity of the exercise sessions.

Frequency: Research has not determined how frequently exercise should be performed for optimal cardiorespiratory improvement. An acceptable recommendation is three times weekly. This schedule permits an adequate period of recovery between activity sessions.

TABLE II

Activities That Improve Endurance of Performance

1. Walking
2. Jogging
   a. In place
   b. Moving
3. Running
4. Cycling
5. Skiing
   a. Alpine
   b. Nordic
6. Swimming
7. Rope skipping
8. Ice skating
9. Roller skating
10. Rowing
11. Bench or stair climbing

Intensity: The intensity of training is critical to improvement in aerobic capacity. The best estimate at this time is that an intensity of 70 percent of a person's maximal aerobic power is sufficient to afford cardiorespiratory gains. Activity performed at a greater intensity produces change, but of a much smaller magnitude. Determining the appropriate intensity of the activity for each individual depends upon the base-line measures obtained during a progressive exercise test. Training regimens can be based on the concept of METS (1 MET = 3.5 ml oxygen/kg per min) or target heart rates. The monitoring of heart rates during activity sessions is important. In an asymptomatic adult, activity heart rates during the endurance phase of training are maintained at levels of 120 to 160 beats/min.

Duration: Cardiorespiratory benefits occur when an exercise session is more than 10 minutes in duration. In programs of prevention, intervention and rehabilitation, sessions are usually 20 to 45 minutes long.

Research indicates that adults reach an optimal training level some time after 20 to 30 weeks of regular physical activity. At approximately 6 months, maximal aerobic power gains tend to plateau. The degree of improvement is related to the state of deconditioning; that is, the lower the level of initial performance capability, the greater the expected improvement.

Adherence: Improvement in endurance, strength and range of joint motion requires adherence to an exercise regimen. Problems of muscle or joint soreness occur frequently. Foot, ankle, knee and back pains are not only irritants but seriously impair attendance and participation. These problems can be minimized if the introduction to an exercise program is gradual. Moderation is important. Occasionally a man reports that his interest has waned because of the monotony of the exercise regimen. Other dropouts from physical activity programs report that the time required for exercise deprived them of time spent on the job or with their family. Complaints of orthopedic problems or monotony can be avoided by skillful exercise leaders and informed physicians who

counsel their patients in the proper selection of activity. The time spent away from one's job or family cannot be avoided, but it is not a large price to pay for improvement in health status.

No one is ever too old to have a good time. Exercise should be a pleasant experience. A preoccupation with distance, number of repetitions or a stop watch may provide incentives but is of secondary importance in adult fitness programs. The primary emphasis should be on participating in activities that are safe and enjoyable. When this goal is achieved, people will sustain and adhere to their exercise commitment.

Conclusions

There is a national awareness of the need to improve the physical fitness of adults. Physical activity of a progressive nature produces functional changes. Through exercise, people can increase their endurance capabilities, muscular strength and range of motion of the joints. A progressive exercise test that includes monitoring of the subject's electrocardiogram and arterial blood pressures is the objective assessment necessary to the exercise prescription. Programs should be designed or recommended to meet individual needs. Special attention should be paid to gradual orientation to the exercise regimen. Initially low levels of energy expenditure are desirable. The concepts of intensity, frequency and duration are important. Adaptation to the stress of exercise requires time. Every effort should be made to support the adult in his participation. Successful patient management rests with the cooperative effort and communication of a patient, his physician and the leader of physical activity.

Before a physician recommends an individual exercise regimen or group program, he should carefully evaluate it. Answers to the following questions are important to his evaluation: Does the program allow for individual differences? Is the subject gradually eased into the exercise program? Are the exercise leaders competent? Is adequate supervision available in programs where participants are at high risk? What factors determine the intensity of the exercise session? Are allowances made for participants who have special medical problems (arthritis, emphysema, diabetes, asthma)? What are the avenues for communication and feedback on the patient's progress?

The assessment of human performance is a science. Individually prescribing activity is an art.

Acknowledgment

I acknowledge the assistance of James Hodgson, Mitchell McKirnan and Gale Miller. Special thanks to Cal Shearburn for his efforts in computing the table of aerobic power estimations.

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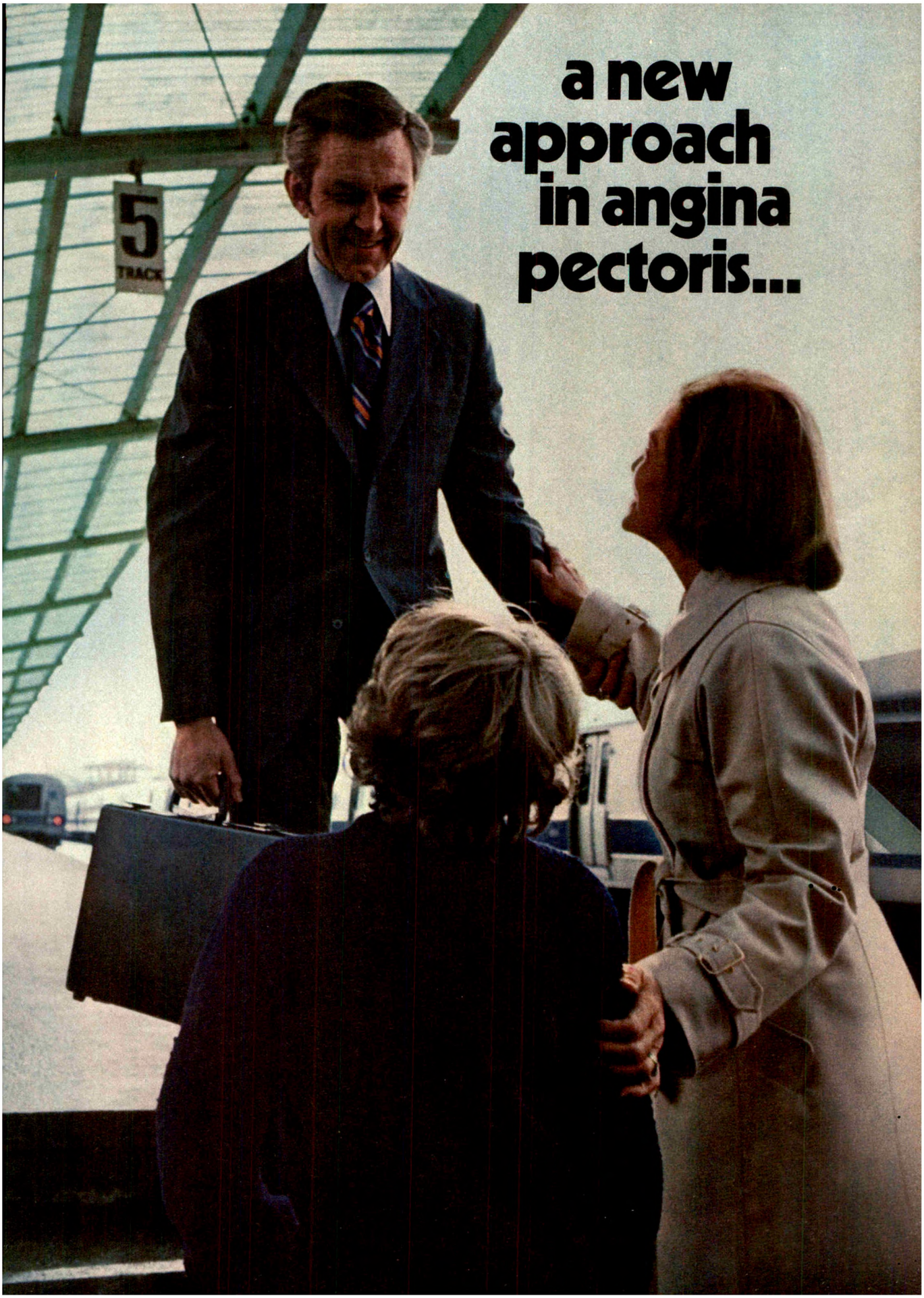
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In 29[1-29] of 30[1-30] controlled clinical trials, INDERAL was found to reduce the incidence of anginal pain and the consumption of nitroglycerin. In 24[1-9,11-15,17,18,20-24,26,27,30] of these studies, it was possible to determine the proportion of patients responding to treatment; approximately 75 percent of the patients had less pain and used less nitroglycerin when taking INDERAL than when taking a placebo. Of the 29 studies reporting effectiveness with INDERAL, results were deemed statistically significant in 19,[1-19] not statistically significant in 2,[20,21] and the statistical significance was not given in 8.[22-29] In these and 3 other studies,[31-33] the effectiveness of INDERAL was demonstrated both clinically and by objective laboratory measurements. One study[30] reported propranolol not effective. Altogether, these clinical studies[1-33] covered 746 patients.

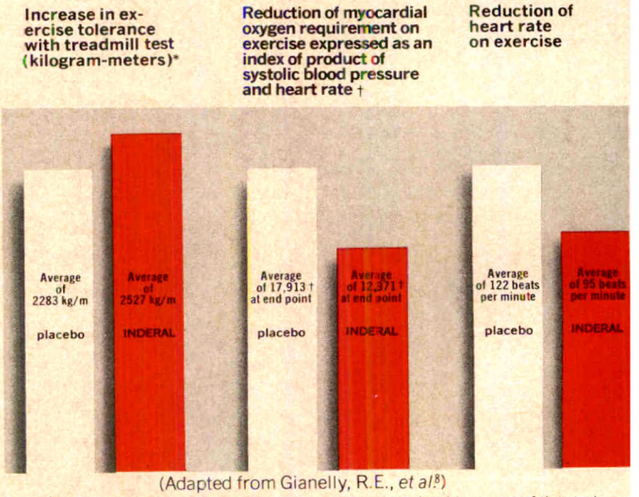
improved exercise tolerance

In 17 controlled trials dealing with exercise tolerance, INDERAL was found to be effective in 14[2,8,10,12,13,15,16,18,22,23,25,27,28,32] and not in 3.[3,29,30] In 8[2,8,10,12,15,16,18,32] of these, the improvement was statistically significant, in 6[13,22,23,25,27,28] the significance was not given.

objective proof of effectiveness

clinical results with 160 mg. Inderal (propranolol hydrochloride) daily in 19 patients

In a double-blind study, the effect of INDERAL on exercise tolerance was examined by Gianelly and associates.[8] It was concluded that in responsive patients, INDERAL, by reducing cardiac work, tends to bring into balance myocardial oxygen supply and need, and increases exercise tolerance.



(Adapted from Gianelly, R.E., *et al*[8])

*Incomplete data on one patient reduced the number to 18 for this aspect of the study.

In a double-blind crossover study of 19 patients with a typical history of angina and a positive Master 2-step test, the effects of INDERAL on exercise tolerance were correlated with cardiovascular physiologic effects. The patients, ranging in age from 38 to 65 years, received either placebo or 160 mg. INDERAL daily in 4 divided doses for 4 weeks. Exercise tolerance was assessed using a treadmill.

in the management of moderate to severe angina pectoris

works to decrease myocardial oxygen demand and prevent oxygen deficit in responsive patients

When physical or psychological stress increases beta-adrenergic stimulation of the heart, oxygen demand may exceed capacity for oxygen delivery in a coronary circulation compromised by atherosclerosis.

INDERAL (propranolol hydrochloride)—through its beta-adrenergic blocking action—provides a unique approach. By specifically competing with catecholamines for available myocardial beta-receptor sites, INDERAL can reduce sympathetically induced increases in heart rate, systolic blood pressure, and velocity of contraction during exercise or stress—and thus decrease the oxygen requirements of the heart. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to the decreased oxygen requirement.

for maximum effect, dosage should be titrated and individualized

The average optimum dosage of INDERAL appears to be 160 mg. per day, although individuals may respond at any dosage level. Starting with 10-20 mg. 3 or 4 times daily, before meals and at bedtime, dosage should be gradually increased at 3 to 7 day intervals until optimum response is obtained. Doses higher than the average optimum dosage of 160 mg. may be required; however, the value and safety of dosage exceeding 320 mg. per day have not been established.

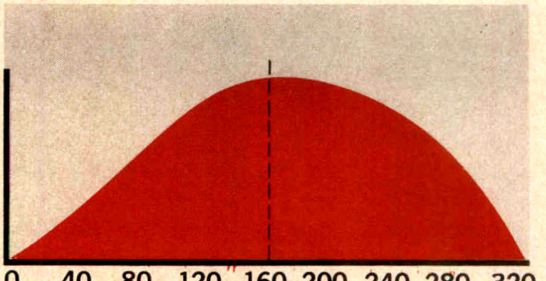
If treatment is to be discontinued, it is recommended that withdrawal be gradual over a period of several weeks. (See PRECAUTIONS.)

Special caution should be observed in patients with heart block or a history of congestive heart failure. (See CONTRAINDICATIONS and WARNINGS.)

Good medical practice dictates that INDERAL should not be continued unless there is reduced pain or increased work capacity. Treatment should be carefully monitored.

INDERAL will not interfere with the cardiac action of sublingual nitroglycerin, or cardiotonic agents such as digitalis.

average optimum daily dosage is 160 mg.



Clinical experience as reported in controlled studies has shown that the average optimum dosage appears to be 160 mg. per day. However, dosage must be individualized as some patients may obtain maximum response at a dosage level lower than 160 mg. daily, and others may require a dosage up to 320 mg. daily. The value and safety of daily doses of more than 320 mg. have not been established. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE OR EXAGGERATED RESPONSE)

USE OF **INDERAL®** /ANGINA PECTORIS
CONTINUED ON NEXT PAGE

(See last two pages of advertisement for prescribing information.)

Ayerst®

Inderal®

(propranolol hydrochloride)

for moderate to severe angina pectoris in responsive patients

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®

Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support or vital functional balances.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergi blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyro-

toxicosis, exercise).

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: *Angina Pectoris Due to Coronary Atherosclerosis.* The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL (propranolol hydrochloride) is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipatating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL (propranolol hydrochloride) should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, non-thrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg. three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. The value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See PRECAUTIONS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE

No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst®

AYERST LABORATORIES
NEW YORK, N. Y. 10017

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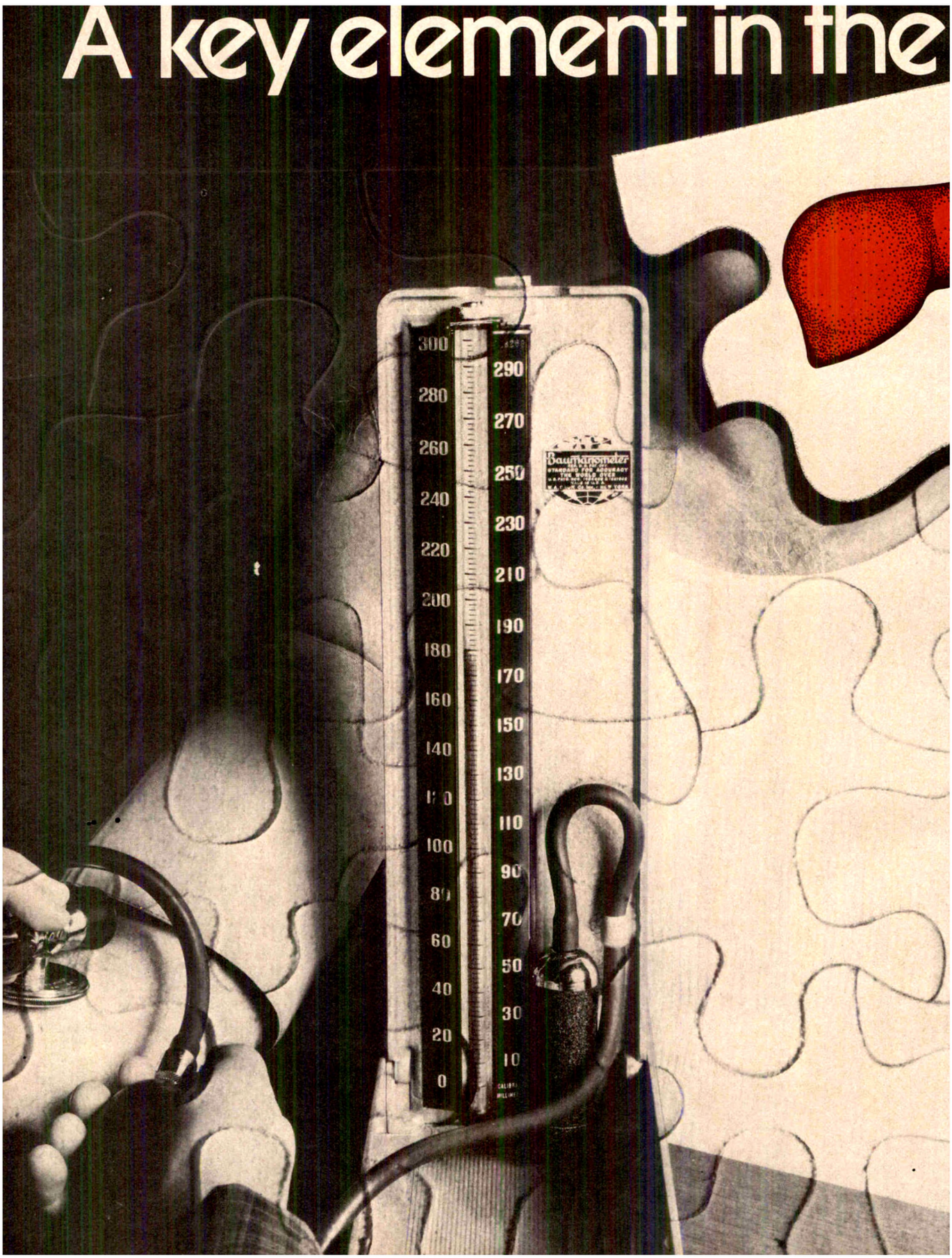
A key element in the
Baumé hydrometer
STANDARD FOR ACCURACY
300
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hypertension puzzle

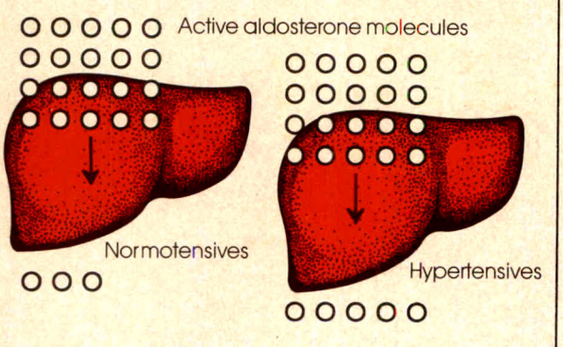
The liver metabolizes significantly less aldosterone in hypertensives than in normotensives.[1,2]

A significantly decreased hepatic MCR (metabolic clearance rate) of aldosterone, without significantly decreased SR (secretion rate), was demonstrated in approximately 90 percent of a group of 56 patients with benign essential hypertension.[1]

Thus "Failure of the aldosterone SR to fully adapt to the decrease in MCR may be responsible for a relative state of hyperaldosteronism in many patients with BEH [benign essential hypertension], even when the secretion and excretion rates are within normal range.

"It is conceivable that it is the mineralocorticoid [aldosterone] excess that is leading to an increase of sodium content in the arteriolar wall and the hypertensive process itself, in many patients with BEH."[2]

Metabolic clearance of aldosterone in hypertensives and in normotensives*



*Schematic representation

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

- Spironolactone blocks the pressor effect of aldosterone at the arteriole,[3-5] and exerts natriuretic action in the distal renal tubule.
- Hydrochlorothiazide exerts additive antihypertensive effect through its action at a different renal site.
- Aldactazide helps maintain potassium balance—without the need for potassium supplements—because the potassium-sparing action of spironolactone offsets the potassium-losing effect of hydrochlorothiazide.

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See following page for brief summary.

To help control the aldosterone factor in essential hypertension

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

Indications—Hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusion may benefit from Aldactazide therapy.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of the renal function. Anuria; sensitivity to thiazides or other sulfonamide-derived drugs. Probably contraindicated in acute or severe hepatic failure.

Warnings—Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Potassium supplementation is recommended only in exceptional instances, but may be considered when a glucocorticoid is also given. Utilize normal dietary sources of potassium if possible when potassium supplementation is necessary. If enteric-coated potassium is used be alert to the possible development of hemorrhagic, stenotic, ulcerated or perforated small-bowel lesions; deaths have occurred. The possibility of exacerbation or activation of systemic lupus erythematosus by sulfonamide derivatives, including thiazides, has been reported.

Administer thiazides with caution to pregnant or lactating patients. Adverse reactions which may occur in the adult (hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, etc.) may possibly occur in the newborn, since thiazides cross the placental barrier and may also appear in breast milk.

Precautions—Consider the possibility of fluid and electrolyte imbalance. Serum and urine electrolyte determinations are particularly important in patients with excessive vomiting or in those receiving fluids parenterally. Medications such as digitalis may also influence serum electrolytes. Warning signs of possible fluid and electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains, cramps or fatigue, hypotension, oliguria, tachycardia, gastrointestinal symptoms. Hypokalemia may develop with brisk diuresis in severe cirrhosis or during the concomitant use of glucocorticoids or ACTH. Inadequate oral electrolyte intake contributes to hypokalemia. Hypokalemia may cause signs of digitalis intoxication with previously tolerated doses of digitalis.

Give Aldactazide cautiously to patients with severe liver disease since thiazides can precipitate hepatic coma; discontinue if mental confusion increases. Consider also other factors that may precipitate hepatic coma, including blood in the gastrointestinal tract or preexistent potassium depletion. Reversible elevation of NPN and BUN may occur in some patients receiving Aldactazide. The most common electrolyte disturbance is dilutional hyponatremia which requires appropriate corrective measures. A true low-salt syndrome is rare; discontinue Aldactazide and administer sodium for this condition.

Although rare, the most potentially serious electrolyte disturbance is hyperkalemia; if this occurs discontinue Aldactazide and restrict potassium intake. Rarely, fatality due to hyperkalemia has been reported. Hyperkalemia is more likely to occur in severely ill patients with relatively small urine output or in patients receiving supplemental potassium; determine serum electrolytes frequently in such patients. Consider the possibility of hyperuricemia or a decrease in tolerance to glucose.

Patients with severely resistant edema may have an increased diuretic response following the addition of a potent glucocorticoid, such as 15 to 20 mg. of prednisone daily, to Aldactazide therapy. Supplemental potassium will usually be necessary in such patients and the usual precautions with glucocorticoids are necessary. Use caution if regional or general anesthesia is necessary since Aldactazide reduces vascular responsiveness to norepinephrine in such patients. Thiazides may increase responsiveness to tubocurarine. The antihypertensive effects of hydrochlorothiazide may be enhanced in patients who have undergone sympathectomy.

Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may increase serum PBI levels without signs of thyroid disturbance.

Adverse Reactions reported with *spironolactone* use: Drowsiness and lethargy, mental confusion, diarrhea and other gastrointestinal symptoms, mild androgenic manifestations (including hirsutism, menstrual irregularity, deepening of the voice), gynecomastia, inability to achieve or to maintain erection, headache, maculopapular or erythematous cutaneous eruptions, urticaria, drug fever, ataxia.

Adverse reactions reported with *thiazide* use: purpura, thrombocytopenia, leukopenia, agranulocytosis, gastrointestinal disorders (anorexia, nausea, vomiting, diarrhea, abdominal cramps), rash, pruritus, paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, urticaria, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness, restlessness. Reduce dosage or withdraw drug whenever adverse reactions are moderate or severe.

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Comparative Response to Isometric (Static) and Dynamic Exercise Tests in Coronary Disease

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Forty-six patients with arteriosclerotic heart disease manifested significant electrocardiographic changes (accompanied by angina in 35) during maximal exercise testing. These patients subsequently performed isometric exercise at levels representing various percentages of maximal voluntary contraction. Twenty-two patients also performed combined isometric and submaximal dynamic exercise. The prevalence rate of S–T segment changes during isolated isometric exercise depended on the percent of maximal voluntary contraction applied but was far lower than the rate observed during maximal dynamic exercise. Angina seldom occurred. Manifestations of coronary insufficiency appeared more often during combined submaximal dynamic and isometric exercise than during isolated isometric testing.

Aortic pressure was measured in eight cases. Tension-time index and pressure-heart rate product were lower when maximal dynamic exercise was stopped owing to coronary insufficiency than at the end of isolated isometric exercise or combined submaximal dynamic and isometric exercise. However, the latter two tests produced fewer ischemic manifestations. The reasons for these discrepancies are discussed. We conclude that isometric exercise tests are unsuitable for diagnosing coronary insufficiency.

Although isometric exercise is a common everyday activity, its hemodynamic effects have not been extensively studied. In normal subjects, the increases in heart rate and blood pressure produced by isometric exercise depend on the percent of maximal voluntary contraction exerted independent of the muscle group involved. At levels greater than 15 to 20 percent of maximal voluntary contraction, hemodynamic response increases linearly until the end of the exercise, greater loads producing greater changes and rapid muscular fatigue.[1] Isometric stress testing may be hampered by the lack of steady state hemodynamic measurements, poor patient cooperation and the subjective nature of determining maximal voluntary contraction, but it is easily and quickly performed, and hemodynamic values return to resting levels shortly after muscular relaxation.

When two isometric loads are applied either simultaneously[2] or successively (personal observation, J-CH), heart rate and blood pressure responses at the end of the test depend on the intensity of the greater and second loads, respectively. The response to combined dynamic and isometric exercise is greater than the response to either test alone.[2]

In this study we investigated the comparative influence of isometric and dynamic exercise on the symptoms, electrocardiogram, tension-time index and pressure-heart rate product of patients with arteriosclerotic heart disease.

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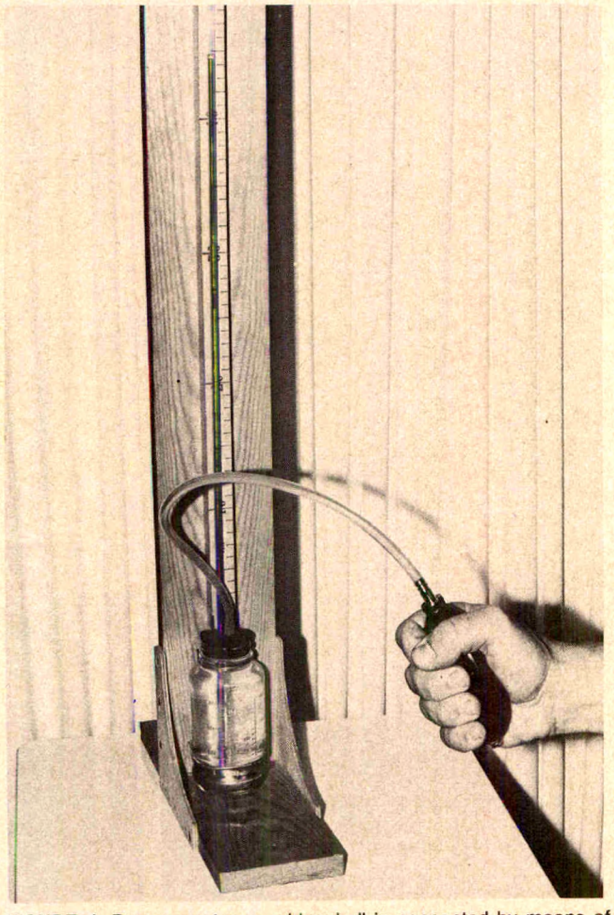

FIGURE 1. Dynamometer: a rubber ball is connected by means of semirigid tubing to a closed chamber, the lower third of which contains mercury. The lower end of a vertically fixed glass tube (inner diameter 2 mm) is placed into the mercury. The upper two thirds of the chamber, rubber ball and tubing are filled with water. When the rubber ball is pressed, mercury is pushed into the glass tube. The small bore of the tube results in a small displacement of mercury volume, thus avoiding any significant dynamic component.

Material and Methods

Material

The study group comprised 46 volunteer male outpatients, aged 36 to 66 years, with arteriosclerotic heart disease. Confirmation of the diagnosis was based on the presence of electrocardiographic signs of old infarction or typical symptoms of angina pectoris. During dynamic exercise testing all patients showed typical S–T segment changes and 35 had angina. No patient had signs of ventricular aneurysm, heart failure, angina, significant arrhythmias or conduction disturbances at rest.

Procedure

Dynamic exercise was performed with patients seated on an electrically braked bicycle ergometer (Elema); loads were increased by 25 watts every 5 minutes until the electrocardiogram showed a horizontal or downsloping S–T segment depression of at least 0.2 mv.[3,4]

Isometric exercise was performed alone or in combination with dynamic exercise. For this purpose we utilized sustained contraction of a handgrip calibrated with a mercury manometer; the tubing had a small bore to avoid any significant dynamic component (Fig. 1). Patients were requested to breathe freely while maintaining their grasp on the handgrip until they experienced exhaustion at 30, 50, 70 or 90 percent of maximal voluntary contraction. The latter was defined as the mean value between the two most powerful contractions in three successive trials. Every patient sustained two different submaximal isometric exercise levels. Mean test durations were, respectively, 265, 125, 63 and 31 seconds at the 30, 50, 70 and 90 percent levels.

Twenty-two patients whose electrocardiogram did not change during isometric exercise were submitted to a dynamic load 25 to 50 watts less than the individual maximal work load; isometric exercise (at 30 or 50 percent of maximal voluntary contraction) was added at the start of the sixth minute of exercise.

The electrocardiogram (leads I, II, V_2 and V_5) was recorded every minute on a four channel Mingograph 34 (Elema). In some patients with angina pectoris a polyethylene catheter (PE 150) was introduced percutaneously through the brachial artery into the ascending aorta and

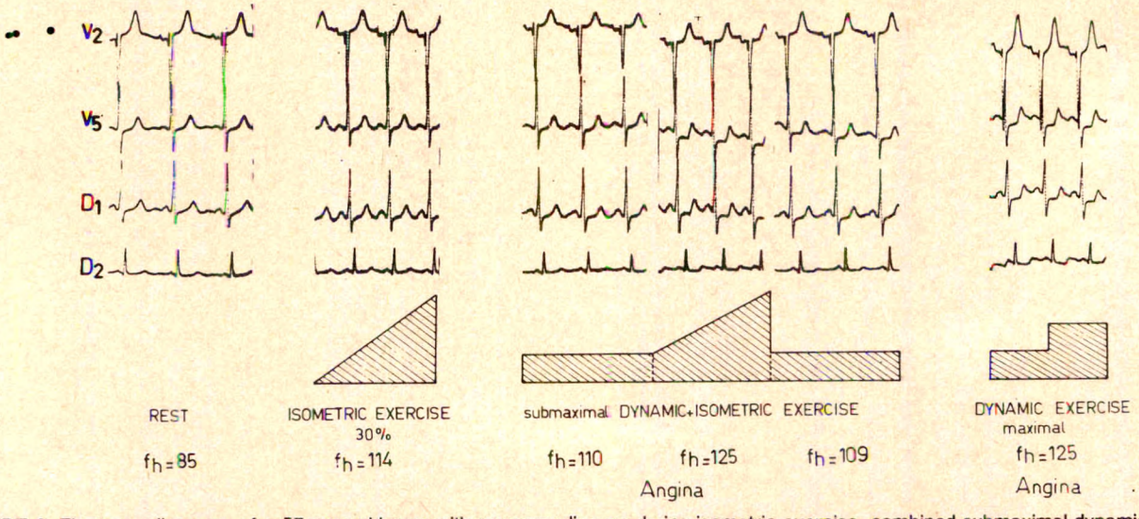

FIGURE 2. Electrocardiograms of a 57 year old man with coronary disease during isometric exercise, combined submaximal dynamic and isometric exercise and maximal dynamic exercise. fh = heart rate.

blood pressure was recorded with a Statham transducer (P23Db), using a Philips amplifier and a Honeywell 1508 Visicorder.

Isometric exercise was performed on the day of the dynamic effort, at least 30 minutes after the electrocardiographic changes disappeared, or several days later. Most patients were tested in the afternoon, 2 or 3 hours after lunch. Patients who underwent intraaortic catheterization performed their exercise in the morning after breakfast, starting with isometric testing and performing dynamic exercise later, at least 30 minutes after the disappearance of electrocardiographic changes.

Results

Heart rate: The increase in heart rate was similar at the end of the four isometric exercise levels performed by 20 patients: 104 ± 3 (standard error of the mean) at 30 percent, 108 ± 3 at 50 percent, 113 ± 3 at 70 percent and 108 ± 4 at 90 percent of maximal voluntary contraction. It was significantly lower ($P < 0.05$ to 0.01) than during maximal dynamic exercise in the corresponding groups (respectively, 120 ± 4, 119 ± 4, 122 ± 4 and 124 ± 5). It was the same after combined maximal dynamic exercise and submaximal dynamic isometric exercise (respectively, 117 ± 4 and 116 ± 4).

Electrocardiogram: S–T segment depression of at least 0.2 mv occurred during maximal dynamic exercise in all 46 patients (and 35 of these patients experienced angina) (Table I). No patient manifested arrhythmias or conduction disturbances. The highest average level attained was 75 watts (range 25 to 125).

During isometric exercise, S–T segment depression was inconstant, occurring in 3 of 20 patients at 30 percent, 7 of 20 at 50 percent and 6 of 20 at 70 percent; no changes were observed at 90 percent of maximal voluntary contraction. These changes usually disappeared within a few seconds after the test was stopped and never occurred during the recovery period. Rare extrasystoles were noted, but no other rhythm disturbances were recorded.

During the combined submaximal dynamic and isometric exercise, S–T segment changes were more frequent, occurring in 15 of 22 cases; in all 15 electrocardiographic changes had not occurred during isolated isometric exercise (Table I). These changes were prolonged, lasting 1 to 8 minutes during the recovery period. Only a few extrasystoles were observed in these patients.

Angina: This symptom appeared during maximal dynamic exercise in 35 of the 46 patients (Table I). Only one of these patients had pain during isometric exercise, at 30 and 50 percent of maximal voluntary contraction. Among 18 patients who had angina during maximal dynamic exercise and no electrocardiographic changes during isometric exercise, 10 had pain during combined submaximal dynamic and isometric exercise. These findings were not due merely to prolongation of submaximal dynamic exercise, because when the latter is maintained after isometric exercise is stopped, pain (and S–T changes) may regress (Fig. 2).

Tension-time index[5] and pressure-heart rate product[6]: These variables were calculated from intraaortic pressure recordings obtained in eight patients who performed maximal dynamic exercise (interrupted by angina), isometric exercise and combined submaximal dynamic and isometric exercise (Tables II and III). Heart rate was lower at the end of isometric exercise than at the end of maximal dynamic exercise (respectively, 108 ± 5 and 114 ± 4), but arterial pressure was significantly greater (respectively, 200 ± 12 and 170 ± 10 mm Hg for systolic pressure, 121 ± 6 and 89 ± 4 mm Hg for diastolic pressure), so that tension-time index and pressure-heart rate product were higher at the end of isometric exercise. The difference is statistically significant for tension-time index (respectively, 4,710 ± 360 and 4,160 ± 280) (Table II). However, all of these patients stopped isometric exercise because of muscular fatigue, and none had angina. During combined submaximal dynamic and isometric exercise, tension-time index and pressure-heart rate product were statistically higher than during maximal dynamic exercise (respectively, 5,200 ± 300 and 4,170 ± 280 for tension-time index, 22,900 ± 1,800 and 19,600 ± 1,400 for pressure-heart rate product) although only five patients experienced angina during the combined dynamic and isometric exercise test (Table III and Fig. 3).

TABLE I

Instances of S–T Segment Changes and Angina During Exercise in Four Groups of 20 Patients and One Group of 22 Patients

	Isometric Exercise (% MVC)				Submaximal Dynamic Plus Isometric Exercise (30 and 50% MVC)
	30	50	70	90	
Patients (no.)	20	20	20	20	22*
S–T depression					
≤0.1 mv	0	3	5	0	0
≥0.2 mv	3	4	2	0	15
Angina†	1‡	1‡	0	0	10
S–T depression ≥0.2 mv during maximal dynamic exercise	20	20	20	20	22
Angina during maximal dynamic exercise	12	15	13	16	18

* None of these patients had electrocardiographic changes during isolated isometric exercise.

† All of these patients had angina during maximal dynamic exercise.

‡ The same patient performed at both 30 and 50 percent of maximal voluntary contraction.

MVC = maximal voluntary contraction.

Discussion

Although isometric exercise tests have been widely used for diagnostic purposes and pathophysiologic

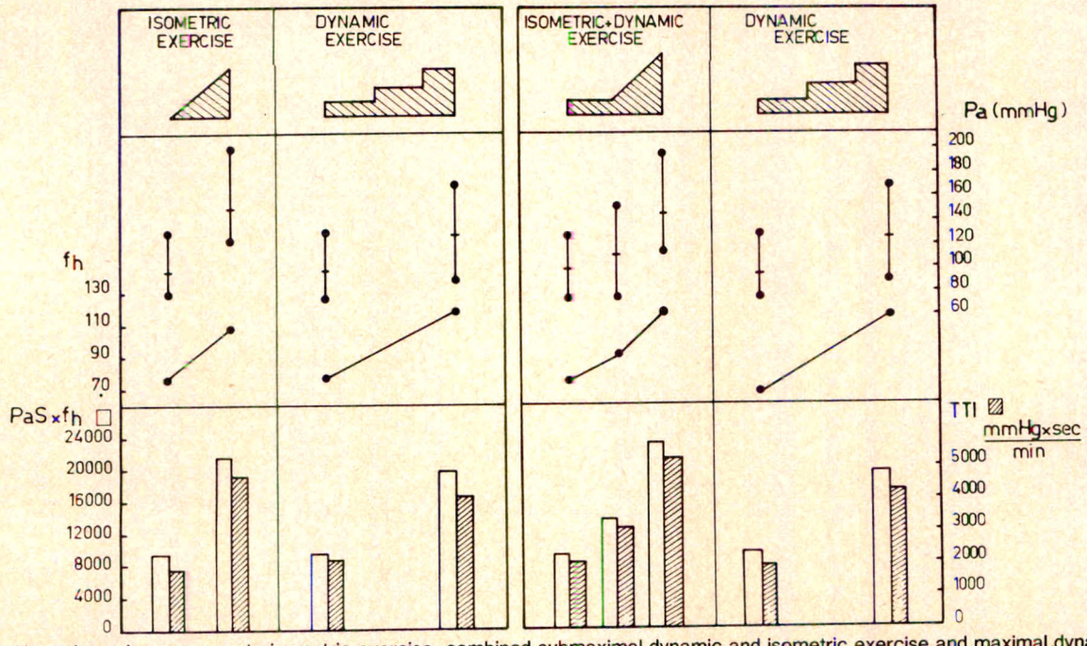

FIGURE 3. Hemodynamic responses to isometric exercise, combined submaximal dynamic and isometric exercise and maximal dynamic exercise in eight patients with angina pectoris (results of Tables II and III). fh = heart rate; Pa = aortic pressure; PaS = systolic aortic pressure; TTI = tension-time index.

TABLE II

Hemodynamic Variables During Isometric and Maximal Dynamic Exercise in Eight Patients with Angina Pectoris*

	Rest	Isometric Exercise	Rest	Maximal Dynamic Exercise
HR	73 ± 3 (7)	108 ± 5 (13)	73 ± 3 (9)	114 ± 4 (10)
APs	131 ± 8 (22)	200 ± 12 (33)	131 ± 8 (24)	170 ± 10 (28)†
APd	78 ± 4 (11)	121 ± 6 (17)	77 ± 3 (10)	89 ± 4 (12)‡
TTI	1,940 ± 140 (400)	4,710 ± 360 (1,020)	2,130 ± 160 (450)	4,160 ± 280 (780)§
APs × HR	9,600 ± 800 (2200)	21,800 ± 1,700 (4,800)	9,600 ± 800 (2,200)	19,400 ± 1,200 (3,500)

Values given are means ± standard error with standard deviation in parenthesis.

APd = diastolic aortic pressure (mm Hg); APs = systolic aortic pressure (mm Hg); HR = heart rate (beats/min); TTI = tension-time index (mm Hg·sec/min).

* Angina always caused the interruption of dynamic testing. No symptoms were caused by isometric exercise. The following variables were significantly higher at the end of the isometric exercise than during maximal dynamic exercise: APs ($P < 0.01$)†; APd ($P < 0.001$)‡ and TTI ($P < 0.05$)§.

TABLE III

Hemodynamic Variables During Submaximal Dynamic Exercise, Combined Dynamic and Isometric Exercise and Maximal Dynamic Exercise in Eight Patients with Angina Pectoris*

	Rest	Submaximal Dynamic Exercise	Submaximal Dynamic + Isometric Exercise	Rest	Maximal Dynamic Exercise
HR	72 ± 5 (13)	90 ± 6 (16)	118 ± 5 (15)	68 ± 3 (10)	113 ± 5 (15)†
APs	126 ± 6 (16)	151 ± 8 (22)	198 ± 10 (29)	127 ± 8 (22)	172 ± 10 (27)†
APd	75 ± 4 (11)	77 ± 4 (10)	111 ± 5 (14)	74 ± 3 (10)	87 ± 4 (12)†
TTI	2060 ± 150 (370)	3,170 ± 260 (730)	5,200 ± 300 (850)	1,960 ± 150 (410)	4,170 ± 280 (800)†
APs × HR	9,200 ± 900 (2,300)	13,800 ± 1,200 (3500)	22,900 ± 1,800 (4600)	8,600 ± 600 (1,800)	19,600 ± 1,400 (4,000)‡

* Angina was the cause for interruption in all dynamic tests and in five combined dynamic and isometric tests. The following variables were significantly higher at the end of combined submaximal dynamic and isometric exercise than during maximal dynamic exercise: APd, APs, HR and TTI ($P < 0.05$)†, and APs × HR ($P < 0.01$)‡. Abbreviations as in Table II.

studies[7–12] in valvular heart disease, their value in ischemic heart disease has been controversial. According to Jackson[13] and Siegel et al.[14] they produce S–T segment changes in one third to one fourth of patients. However, Atkins et al.[15] cited significant S–T changes in only 2 of 11 patients, and Kivowitz et al.[12] observed no angina in 13 cases. In our series, typical S–T segment changes during isometric exercise occurred in one third of the patients with a normal resting electrocardiogram, and angina developed in only 1 of the 35 patients. The discrepancies in these findings could be due to differences in intensity of isometric exercise, which ranged from 20 to 100 percent of maximal voluntary contraction in the various series. In our experience, however, the prevalence of S–T changes is similar between 30 and 70 percent of maximal voluntary contraction; at 90 percent the absence of ischemic myocardial manifestations is essentially caused by an excessively short stress tolerance. Probably more important are differences in the criteria of exercise intolerance: During isometric exercise many patients report vague chest pain although they have no S–T changes; such findings may or may not be diagnosed as coronary insufficiency.

Rhythm disturbances were infrequent during isometric exercise in our series as in those of others,[10,11,16] in contrast to the findings of Atkins et al.[17] We have no explanation for this inconsistency. Nevertheless, we recommend a conservative approach in evaluating the safety of isometric exercise in patients with coronary artery disease.

Myocardial function during isometric vs. dynamic exercise: Isometric exercise tests are relatively innocuous. This is surprising since they produce significant arterial hypertension; the increment in aortic pressure found in our patients was similar to that found by Lind et al.[1] in normal subjects. Tension-time index and pressure-heart rate product have been proposed as indexes of myocardial oxygen consumption. But we have found that these values are lower during maximal dynamic exercise producing angina than at the end of isometric exercise, although the latter exceptionally produces signs of coronary insufficiency when performed alone and frequently (about 50 percent of patients) when performed in combination with submaximal dynamic exercise.

It is possible that these indexes are not fully representative of myocardial oxygen consumption, especially during exercise.[18] Other determinants of cardiac metabolism—heart rate, cardiac output, ventricular wall tension and contractility—may play a role.[19] Moreover, myocardial energy requirements being equal, adaptation of coronary circulation could be different during isometric and dynamic exercise, resulting in different electrocardiographic responses. Finally, the duration as well as the intensity of the myocardial stress should be considered. The duration of dynamic exercise, presumably resulting in accumulation of an oxygen debt, is to a great extent responsible for both angina and S–T segment changes. Near maximal work loads are carried out for a longer period with dynamic than with isometric exercise. Since no steady hemodynamic state is reached during isometric exercise, the heavy myocardial stress caused by this test is of very short duration compared to that seen in dynamic effort. This is certainly why this method of stress rarely elicits evidence of latent coronary insufficiency.

Clinical implications: Our study demonstrates that isometric exercise testing is not suitable for diagnosing coronary insufficiency. The prevalence of S–T segment changes or angina is small during isolated isometric exercise compared to maximal dynamic exercise, but is somewhat greater during combined submaximal dynamic and isometric exercise.

These results are surprising since values for tension-time index and pressure-heart rate product were higher at the end of isometric exercise, isolated or coupled with submaximal dynamic exercise, compared to values found at the end of maximal dynamic exercise. Thus, individually considered, these indexes do not explain the relatively good tolerance for isometric testing manifested by our patients with coronary disease. The duration of maximal stress to which the heart is exposed may be a factor since this period is much shorter in isometric exercise than in dynamic effort.

Acknowledgment

We thank Dr I. Ohr for his help in the English translation of this text.

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Comparison of the Two-Step and Maximal Exercise Tests in Patients with Coronary Artery Disease

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This study has investigated the claim that the electrocardiographic response to the maximal exercise test provides a more accurate method of assessing the presence and severity of coronary artery disease than the electrocardiographic response to the two-step test. One hundred and one men with a chest pain syndrome underwent the two-step test, maximal exercise test and coronary angiography during the same admission. There was a preponderance of men who performed the maximal exercise test as a result of a negative two-step test. A positive two-step test was defined as horizontal or downsloping S–T segment depression of 0.5 mm or more, whereas a positive maximal exercise test was defined as similar S–T segment depression of 1.0 mm or more. Of the 17 men with no or insignificant coronary artery disease, 5 had a positive two-step test and 6 a positive maximal exercise test. Of the 84 men with coronary artery disease, 33 had a positive two-step test and 38 a positive maximal exercise test. Thus, the specificity of the two-step test for coronary artery disease was 87 percent and that of the maximal exercise test was 86 percent; the respective sensitivity rates were 39 and 45 percent. The percentage of positive results of both exercise tests increased similarly with the severity of coronary artery disease.

Nine patients, eight of whom had coronary artery disease, had a positive maximal exercise test but a negative two-step test; in these patients the maximal heart rate was significantly higher during the maximal exercise test than during the two-step test. Five patients, all with coronary artery disease, had a positive two-step test but a negative maximal exercise test. One patient manifested 0.5 mm S–T segment depression in both tests and was thus judged to have a positive two-step test and a negative maximal exercise test. In another patient results were positive in lead V_4 of the two-step test, a lead not recorded in the maximal exercise test. The other three patients had had positive results in a second maximal exercise test recorded in the supine position, thus demonstrating that in certain cases the effects of augmented venous return in the supine position may be as important a factor in eliciting ischemia as the achieved heart rate.

There has been a recent tendency to replace the two-step exercise test with submaximal[1–3] or maximal[3–5] exercise testing for evaluation of patients with chest pain. It has been claimed not only that the work load of the two-step test is relatively light, and therefore insufficient to detect lesser degrees of coronary artery disease, but also that the maximal exercise test allows for better quantification and control of stress applied to the patient. For a definitive answer on the relative merits of the two-step and maximal exercise tests in detection of coronary artery disease, both tests must be performed in the same group of patients whose coronary anatomy has been defined. In this study we carried out such an investigation, and the results form the basis of our report.

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TABLE I

Sensitivity and Specificity of Exercise Criteria

Results of Exercise Test	Results of Coronary Angiography: CAD	NCAD
Positive	A	B
Negative	C	D

Sensitivity of exercise criterion = A/(A + C) expressed as percent.

Specificity of exercise criterion = A/(A + B) expressed as percent.

Thus, false positive results = 100 — specificity; false negative results = 100 — sensitivity.

CAD = coronary artery disease; NCAD = no or insignificant coronary artery disease.

TABLE II

Comparison of the Two-Step and Maximal Exercise Tests

Patients (no.)	S–T Segment Depression: Two-Step Test: None no.	%	0.5–1 mm no.	%	>1.0 mm no.	%	Maximal Exercise Test: None no.	%	≥1.0 mm no.	%
NCAD(17)	12	70.5	4	23.5	1	6.0	11	64.8	6	35.2
CAD(84)	51	60.7	11	13.1	22	26.2	46	55.0	38	45.0

CAD = patients with coronary artery disease; NCAD = patients with insignificant coronary artery disease or no disease; no. = number of patients.

TABLE III

Sensitivity and Specificity of the Two-Step and Maximal Exercise Tests

	Sensitivity (%)	Specificity (%)
Two-step test		
0.5 mm S–T depression	39	87
1.0 mm S–T depression	26	97
Maximal exercise test (1.0 mm S–T depression)	45	86

Materials and Methods

The study group comprised 101 men with a chest pain syndrome. Their average age was 47 years. All patients underwent the two-step test, maximal exercise test and coronary angiography during the same admission. There was a preponderance of men with negative two-step tests who had subsequent maximal exercise tests. The two exercise tests were usually performed on the same day with the two-step test preceding the maximal exercise test by 1 hour. Standard 12 lead electrocardiograms were recorded with patients in the supine position before, immediately after and during the 3rd, 5th and 8th minutes after the two-step test.[6] The maximal exercise test was performed on a bicycle ergometer. The initial work load was 300 kilopond-meters (kpm) and this load was increased by 150 kpm every 3 minutes until the patient manifested chest pain, fatigue or marked ventricular arrhythmia. Seven lead electrocardiograms were recorded with the patient sitting on the bicycle; the six limb leads and lead V_5 were recorded at the same time intervals as those used during the two-step test. In addition, lead V_5 was monitored throughout exercise and recorded for 10 seconds at the end of every minute of exercise.

A positive two-step test was defined as horizontal or downsloping S–T segment depression of 0.5 mm or more.[7] A positive maximal exercise test was defined as horizontal or downsloping S–T segment depression of 1.0 mm or more on the basis of previously published criteria for such tests.[1–3] The latter criterion has been advocated as providing the optimal levels of specificity and sensitivity for S–T segment change during a maximal exercise test.[4]

Coronary arteriography was usually performed on the day after exercise testing. The technique of angiography used in this laboratory has been described previously.[8] Obstructive lesions were defined as those occluding 75 percent or more of the vessel lumen, as estimated by the combined dimensional analysis of the two oblique views. Patients with obstructive lesions of one, two or three major coronary arterial systems comprised the group with coronary artery disease. The group with normal coronary arteriograms included some patients with minor luminal irregularities as well as those without evidence of atherosclerosis.

Sensitivity and specificity were analyzed as shown in Table I.

Results

There were 84 men with coronary artery disease and 17 men with normal coronary arteries. The patients with coronary artery disease were further classified into those with one, two or three vessel disease—28, 26 and 30 patients, respectively.

Detection of coronary artery disease and exercise tests (Tables II and III): The 17 patients with normal coronary arteries had five positive two-step tests and six positive maximal exercise tests. The 84 patients with coronary artery disease had 33 positive two-step tests and 38 positive maximal exercise tests. When 1 rather than 0.5 mm S–T segment depression was taken as a criterion for a positive two-step test, only 22 patients with coronary artery disease and 1 with normal coronary arteries exhibited such a response. Thus, the sensitivity in detection of coronary artery disease of a positive two-step test based on a criterion of 0.5 mm S–T segment depression was 39 percent compared with 45 percent for a positive maximal exercise test. The specificity of the two-step test was 87 percent and that of the maximal exercise test 86 percent. If a 1 mm criterion was taken for a positive two-step test, the specificity was 97 percent but the sensitivity decreased to 26 percent.

Severity of coronary artery disease and exercise tests (Tables IV and V): The percentage of positive tests increased with the severity of coronary artery disease. However, the sensitivity levels of the two-step and maximal exercise tests were similar for all degrees of coronary artery disease and demonstrated no statistical difference.

TABLE IV

Comparison of the Two-Step and Maximal Exercise Tests in Patients with Different Degrees of Coronary Artery Disease

Patients (no.)	S–T Segment Depression									
	Two Step Test						Maximal Exercise Test			
	None		0.5–1.0 mm		>1.0 mm		None		>1.0 mm	
	no.	%	no.	%	no.	%	no.	%	no.	%
1VD (28)	22	78.6	4	14.3	2	7.1	22	78.6	6	21.4
2VD (26)	15	57.7	4	15.4	7	26.9	11	42.3	15	57.7
3VD (30)	14	46.7	3	10.0	13	43.3	13	43.3	17	56.7

1VD = obstructive disease of one major coronary arterial system; 2VD = obstructive disease of two major coronary arterial systems; 3VD = obstructive disease of three major coronary arterial systems; no. = number of patients.

Variance in results between exercise tests (Tables VI and VII): Five patients had a positive two-step test and a negative maximal exercise test. All patients in this category had coronary artery disease. In three patients of this group, the achieved heart rate was higher during the maximal exercise test than during the two-step test, and in two patients the same heart rate was achieved during both tests.

To explain the results in these five patients, individual case analysis was performed. The first patient had 0.5 mm S–T depression on both tests and was therefore considered to have a negative maximal exercise test. Another patient manifested S–T depression only in lead V_4 after the two-step test, and this lead was not recorded during or after the maximal exercise test. Neither of these explanations applied to the other three patients who therefore underwent a second maximal exercise test. The electrocardiogram after the second maximal exercise test was recorded with the patient lying supine instead of sitting on the bicycle. In all three cases, the second maximal exercise test was positive.

Nine patients, one with normal coronary arteries, had a positive maximal exercise test and a negative two-step test. In these patients the maximal mean heart rates in the two-step and maximal exercise tests were 88 and 134 beats/min, respectively ($P < 0.05$).

Discussion

The purpose of our study was to compare the diagnostic value of the two-step and the maximal exercise tests in symptomatic patients. Our results show that the sensivitity and specificity of the two tests are very similar when the S–T segment criteria defined earlier are used. In addition, we have confirmed the results of reports[4,8,9] showing that if 1.0 mm S–T segment is used as a positive end point for the two-step test, the sensitivity markedly decreases but the specificity becomes greater.

The sensitivity ranges between 35 and 84 percent[4,8–10] depending in part on the criteria used for heart rate and S–T segment depression. The lower levels of sensitivity reported in our study may repre-

TABLE V

Sensitivity of the Two-Step and Maximal Exercise Tests in Patients with Coronary Artery Disease

	Sensitivity (%)		
	1VD	2VD	3VD
Two-step test			
0.5 mm S–T depression	22.4	42.2	53.3
1.0 mm S–T depression	7.2	27.0	43.3
Maximal exercise test (1.0 mm S–T depression)	22.4	58.0	56.6

Abbreviations as in Table IV.

TABLE VI

Achieved Heart Rate and S–T Segment Depression in Patients with a Positive Two-Step Test and a Negative Maximal Exercise Test

Case no.	Severity of CAD	Two Step Test		Maximal Exercise Test	
		HR	S–T Depression	HR	S–T Depression
1	1 VD	60	0.5	132	0.5
2	1 VD	120	0.5	175	0.0
3	2 VD	88	1.0	135	0.0
4	3 VD	120	1.0	120	0.0
5	3 VD	105	2.0	105	0.0

CAD = coronary artery disease; HR = heart rate (beats/min); other abbreviations as in Table IV.

TABLE VII

Achieved Heart Rate in Nine Patients with a Positive Maximal Exercise Test and a Negative Two-Step Test

Test	Heart Rate (beats/min)
Two-step test	88 (68–100)
Maximal exercise test	134 (88–100)
P value	<0.05

sent inadvertent error in sampling of patient population, and particularly the low level of heart rate achieved in some subjects (Tables VI and VII). The prevalence of false positive results is similar to that reported by Kemp et al.[11] in patients with angina pectoris and normal coronary arteries.

One of the main objections to the two-step test is that it cannot detect mild or moderate degrees of coronary artery disease. From the analysis of our results, it is evident that neither the two-step test nor the maximal exercise test is of great help in the diagnosis of coronary artery disease in patients with single vessel disease, but both tests are more sensitive in multivessel disease.

An important finding is that in individual patients the results of the two-step and maximal exercise tests may differ. It is reasonable to assume that the occurrence of a positive maximal exercise test after a negative two-step test in nine cases was a result of the higher heart rate achieved during the maximal exercise test and the recording of electrocardiograms during and after exercise. The positive two-step test but negative maximal exercise test of five patients is more difficult to explain. In one case, 0.5 mm S–T depression occurred with both tests, and the results were interpreted as a positive two-step test but a negative maximal exercise test. In another case, the recording of only seven leads during the maximal exercise test prevented detection of the ischemic response observed in lead V_4 of the two-step test lead system. In the remaining three cases, it could be shown that the results were influenced by the recording of the electrocardiogram with the patient in the supine position after the two-step test but in the upright position after the maximal exercise test. When the initial maximal exercise test was negative after a two-step test had been positive, a second maximal exercise test was performed in which the electrocardiogram was recorded after exercise with the patient supine. Each of the three patients had an ischemic response not seen previously. This finding suggests that, in certain subjects, the effects of augmented venous return in the supine position[12–15] in increasing cardiac mechanical activity through the Starling effect may be as important a factor in eliciting ischemia as achieved heart rate.[16]

Our results have the following implications for practice: (1) In the majority of cases of chest pain, the sensitivity and specificity of the two-step and maximal exercise tests for coronary artery disease are similar. (2) Patients with an inadequate increase of heart rate after the two-step test should perform a maximal exercise test or, in an alternative practical approach for use in the physician's office, continue the two-step test until higher heart rates are achieved (110 to 120 beats/min). (3) The electrocardiogram should be recorded with the patient in the supine position after exercise if a maximal exercise test is used.

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Arm-Crank Ergometry: A New Method for the Evaluation of Coronary Artery Disease

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We have developed an electrocardiographic stress test to evaluate coronary heart disease using an arm-crank device (modified bicycle ergometer) in patients unable to perform leg exercise. With an initial work load of 200 kg-m/min at 40 revolutions/min for 3 minutes, followed by 100 kg-m/min increments every 3 minutes to a maximum of 700 kg-m/min at the same speed, a linear relation between the increase in heart rate and work load was observed. Twenty-one patients underwent both conventional treadmill exercise (modified Bruce protocol) and arm-crank exercise on separate days. Peak heart rate was slightly slower with arm-crank exercise (81 ± 4 [standard error] vs. 85 ± 3 percent of maximal predicted heart rate for age, $P < 0.02$) but peak systolic blood pressure and heart rate-systolic blood pressure product (double product) did not differ significantly (157 ± 7 vs. 154 ± 6 mm Hg, $P > 0.5$) and (22.0 ± 1.2 vs. 22.5 ± 1.2 × 10^3, $P > 0.1$). Ten patients with documented coronary artery disease, including 7 with angina pectoris, had an ischemic S–T segment response (0.08 second depression greater than 1 mm) by both methods and 10 patients (7 with previous myocardial infarction and 3 with normal coronary arteriograms) had negative results by both techniques. One patient with normal coronary arteriograms had a negative arm-crank test and a positive treadmill test. In 26 patients unable to perform leg exercise the mean peak heart rate, systolic blood pressure and double product with arm-crank exercise were not significantly different ($P > 0.05$) from those achieved by the ambulatory patients (73.2 ± 1.9 vs. 81.0 ± 4.0 percent, 167 ± 8 vs. 157 ± 7 mm Hg and 22.4 ± 1.2 vs. 22.0 ± 1.4 × 10^3, respectively). Six of 26 patients unable to perform leg exercise had a positive arm-crank test. Four of these six patients had angina pectoris and three had a previous myocardial infarction. We conclude that arm-crank exercise is comparable to treadmill exercise and is a reliable alternative method for the evaluation of suspected coronary artery disease in patients unable to perform leg exercise.

Exercise electrocardiography is of considerable value in the diagnosis and functional evaluation of patients with known or suspected ischemic heart disease.[1,2] However, currently available techniques, including the two-step, treadmill, escalator and bicycle ergometer tests, all require leg exercise. Thus, these methods are not applicable to a large population of patients at risk from ischemic heart disease who also have peripheral vascular disease, large joint arthritis, amputations or neuromuscular problems involving the lower limbs. A number of these patients will become potential candidates for elective surgical procedures of various types. The recognition of significant ischemic heart disease in these patients either may serve as a relative contraindication to certain surgical procedures or may aid perioperative management. In addition, in some patients angina pectoris is precipitated primarily by arm exertion. Accordingly, we have devised

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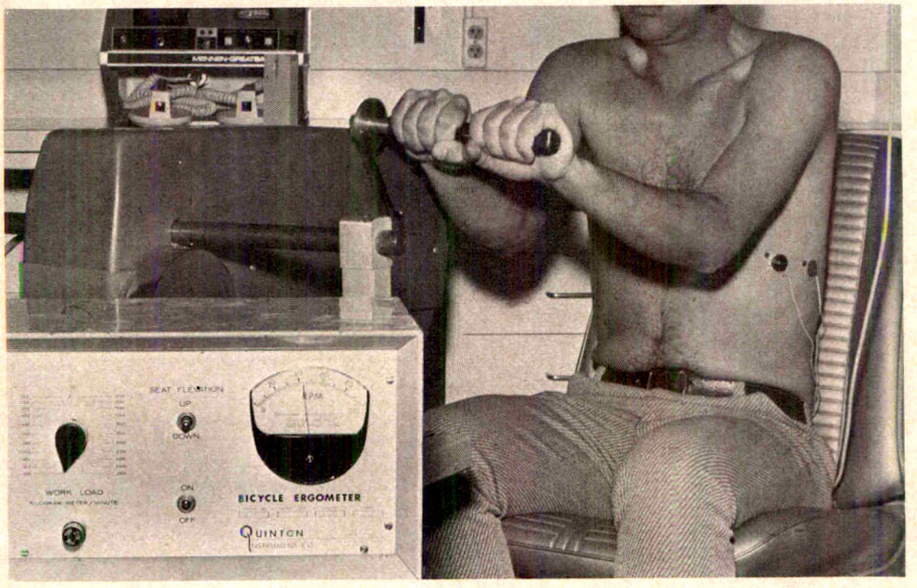

FIGURE 1. The arm-crank device in operation. The fulcrum is at shoulder level of the seated subject who cranks clockwise against a variable torque by turning a 10 inch long steel shaft fitted with two molded plastic handgrips. An electrocardiographic machine is available for constant monitoring.

a graded arm-crank exercise test that permits clinical evaluation of patients unable to perform leg exercise.

The purposes of this study were (1) to devise a program of graded arm-crank exercise combined with electrocardiographic monitoring in a fashion analogous to that of standard tests utilizing leg exercise, (2) to compare the results of such arm exercise with the results of conventional treadmill exercise in patients capable of performing the latter, and (3) to determine the applicability of an arm exercise test for evaluating patients unable to perform leg exercise.

Methods

Forty-seven patients were studied by arm-crank ergometry. There were 7 women and 40 men ranging in age from 41 to 74 years (mean age 57 years). Twenty-one patients were able to perform both arm-crank and treadmill exercise, and 26 patients were able to perform arm-crank exercise only. The 21 patients able to perform both tests included 17 patients with a documented myocardial infarction and 4 patients with atypical chest pain who had normal coronary arteriograms. The diagnosis of myocardial infarction was made on the basis of (1) a history of typical prolonged chest pain, (2) electrocardiographic changes indicative of acute myocardial injury with subsequent evolution of a typical infarction pattern with diagnostic Q waves, and (3) characteristic elevation of serum enzyme levels (creatine phosphokinase [CPK], glutamic oxaloacetic transaminase [SGOT] or lactic dehydrogenase [LDH]). Three of the 17 patients with a prior myocardial infarction had coronary arteriograms that were diagnostic of significant obstructive disease (greater than 50 percent stenosis of one or more major coronary arteries). The 26 patients who could perform only arm-crank exercise included 14 patients with arteriosclerotic peripheral vascular disease, 4 patients with arthritis affecting the legs, 2 patients with amputated legs, 4 patients with a hip prosthesis and 2 patients with neurologic disease. Six of these patients had a documented previous myocardial infarction, and one additional patient had angiographically documented coronary artery disease.

All patients had a complete history and physical examination. A standard 12 lead electrocardiogram was obtained immediately before each exercise test. No patient was tested who had a myocardial infarction within 3 months, an acute febrile illness or unstable angina pectoris. No patient had received a digitalis preparation within 10 days before the study and, in three patients receiving propranolol, this drug was discontinued at least 48 hours before the study.[3] Subjects who were able to perform treadmill exercise performed arm-crank and treadmill tests on separate days, and the order of the tests was randomly alternated. All patients were studied in the postabsorptive state.

The arm-crank device (Fig. 1) consisted of a modified Quinton bicycle ergometer mounted so that the fulcrum of the crank was at shoulder level when the subject was seated. A single pedal on the 6 1/2 inch long radial arm was replaced by a 10 inch long steel shaft fitted with two molded plastic handgrips. The ergometer was so positioned that the subject cranked clockwise with both arms against a variable torque from a seated position. The seat to arm-crank distance was adjusted for each patient to permit coordinated trunk movement with arm-cranking. The graded exercise program, selected empirically after trials in volunteer subjects, consisted of an initial external work load of 200 kg-m/min sustained for 3 minutes, followed by 100 kg-m/min increments every 3 minutes. Cranking speed was maintained at 40 revolutions/min. The highest work load achieved was 700 kg-m/min. The electrocardiogram was monitored during and after the test utilizing fluid-column electrodes for modified leads CR_5 and CR_6. The right lead was placed just medial to the upper scapula posteriorly. The ground electrode was placed just below the right costal margin, and the CR_5 and CR_6 electrodes were located in their usual precordial positions. Leads CR_5 and CR_6 were recorded at 1 minute intervals during exercise and also after exercise until the heart rate had returned to 100 beats/min or less. The systemic arterial pressure was measured by cuff sphygmomanometer immediately before and within 5 seconds of the conclusion of exercise. Treadmill

exercise testing was performed utilizing a modified Bruce protocol.[1] The lead system and recording techniques were identical to those used in the arm-crank test.

Electrocardiographic criteria used for scoring each test as positive or negative were those proposed by Sheffield and co-workers.[4] An ischemic response was defined as the conversion of isoelectric to depressed S–T segments during or after exercise. Depression of the S–T segments was considered to be significant when there was at least 0.1 mv of J point depression and the slope of the first 80 msec of the S–T segment toward the base line was less than 1 mv/sec.[4] Either test was discontinued by the monitoring physician if ischemic changes on the electrocardiogram occurred, if 90 percent of the maximal predicted heart rate was achieved or if chest pain, dyspnea or fatigue precluded further exercise. Before treadmill exercise, control tracings were obtained in all patients in both the seated and standing positions as well as during hyperventilation while standing. Before arm-crank exercise, tracings were obtained with patients in the seated position at rest and during hyperventilation. Data were analyzed utilizing standard statistical methods.[5]

Results

Arm-Crank Ergometry

No patient experienced any difficulty initiating arm exercise with this device. The duration of exercise ranged from 1.67 to 20 minutes and averaged 8.2 ± 0.7 (standard error) minutes. Fourteen of the 47 patients were able to exercise 9 minutes or longer (stage III or better). In these 14 patients, there was a linear relation between heart rate and work load (Fig. 2). No significant training effect was observed in six subjects who performed two arm-crank tests several days apart.

The need to place the lead system in close proximity to exercising muscle groups caused some base-line movement artifact that rarely precluded interpretation during exercise and could often be reduced by fastidious electrode preparation. No recording problems were encountered after exercise was stopped. The only complication encountered with arm-crank exercise occurred in one patient who experienced painful forearm muscle cramps.

Comparison with Treadmill Exercise

Electrocardiographic response: Of the 21 patients who performed both tests, 10 demonstrated ischemic S–T segment responses to both arm-crank and treadmill exercise; 10 additional patients had a negative response to both tests. There was only one discordant S–T segment response. This occurred in a 45 year old man with a normal left ventriculogram and normal coronary arteriograms who had a positive treadmill test at a maximal heart rate-systolic blood pressure product (double product) of 17.2×10^3 and a negative arm-crank test at a double product of 19.2×10^3.

Hemodynamic response: The duration of exercise was slightly longer with the arm-crank test (8.0 ± 0.7 vs. 6.6 ± 0.6 minutes) but the difference was not significant ($P > 0.1$, paired t test). The maximal heart rate (expressed as percent of maximal predicted heart rate for age) was slightly slower with arm-crank exercise than with treadmill exercise (81 ± 4 vs. 85 ± 3 percent), but this difference was of borderline significance ($P < 0.02$). Peak systolic blood pressure and double product in the two tests did not differ significantly (157 ± 7 vs. 154 ± 6 mm Hg, $P > 0.5$) and (22.0 ± 1.2 vs. $22.5 \pm 1.2 \times 10^3$, $P > 0.1$). Figure 3A displays the paired cardiovascular responses in the patients with positive exercise tests and Figure 3B shows the same variables in patients with negative responses to exercise. As with findings for the total group, there was no significant difference between the paired cardiovascular responses of patients with either positive or negative tests.

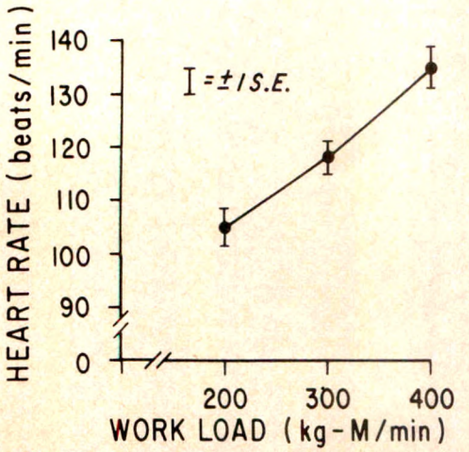

FIGURE 2. The linear relation between absolute heart rate and work load in 14 patients undergoing arm-crank exercise. S.E. = standard error.

Arm-Crank Ergometry in Patients Unable to Perform Leg Exercise

Arm-crank exercise was used to evaluate 26 patients unable to perform leg exercise. These patients achieved a lower heart rate and a higher peak systolic blood pressure than the ambulatory patients, but the differences were not significant (73.2 ± 1.9 vs. 81.0 ± 4.0 percent, $P > 0.05$ and 167 ± 8 vs. 157 ± 7 mm Hg, $P > 0.1$). The double products were virtually identical when the responses of nonambulatory and ambulatory patients were compared (22.4 ± 1.2 vs. $22.0 \pm 1.4 \times 10^3$, $P > 0.5$).

Eight of the 26 nonambulatory patients had typical symptoms of angina pectoris and 4 had a positive arm-crank test; 3 of these 4 had a prior myocardial infarction. Of the four patients with angina who had negative tests, one had coronary artery disease documented by angiography and another had a previous myocardial infarction. However, the double products in the patients with negative tests ranged from 12.5 to 14.0×10^3 in contrast to a range of 21.7 to 26.1×10^3 in the group with positive tests.

The remaining 18 patients underwent arm-crank exercise for various reasons including atypical chest pain and arrhythmia evaluation. Two of these pa-

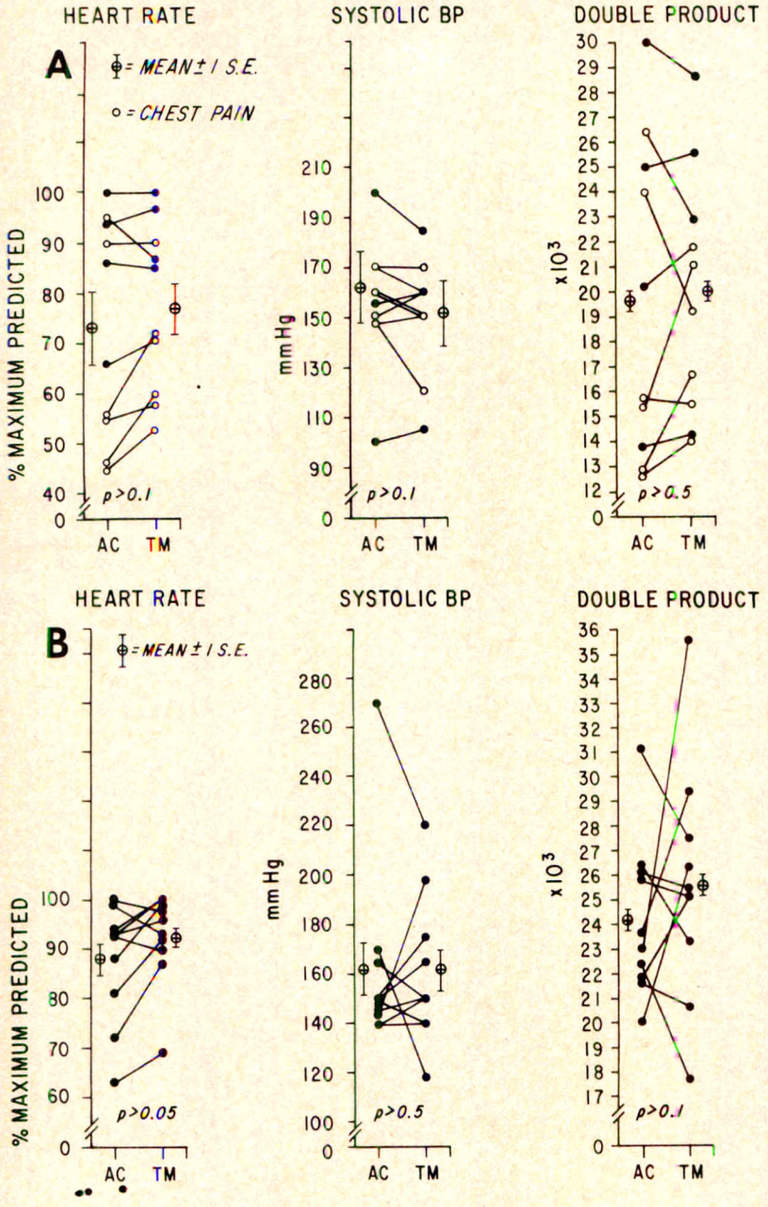

FIGURE 3. Data on heart rate (as percent of the maximal predicted heart rate for age), systolic arterial pressure and double product (absolute heart rate × systolic arterial pressure) in the 10 patients who had positive responses to both tests **(A)** and the 10 patients who had negative responses to both tests **(B).** The data show no significant differences between values obtained during the two tests. AC = arm-crank; BP = blood pressure; S.E. = standard error; TM = treadmill.

tients had positive tests but coronary arteriograms were not obtained because the patients were not considered candidates for coronary arterial surgery. Sixteen of these 18 patients had negative arm-crank studies, including two patients with prior myocardial infarction who had no history of angina pectoris. The range of double products in this group was 14.0 to 32.6×10^3 and the mean was $22.4 \pm 1.8 \times 10^3$.

Discussion

Arm-crank exercise has been extensively investigated in normal subjects[6–8] and has been reported to produce higher heart rates and blood pressures than equivalent work loads with leg exercise in such persons[9,10] and in patients with suspected coronary artery disease.[11] These findings have been used to explain the occurrence of angina pectoris exclusively with arm exercise in certain patients. In our patients we found no significant difference between arm and leg exercise with respect to heart rate and blood pressure at the end of exercise. Previous investigations have used a double-handled cranking device that required the arms to move in opposite directions. With this type of device, considerable static work must be performed by the trunk muscles. By contrast, in our technique the two arms and trunk move together, a method that is more efficient.[12] Thus, the dynamic use of arm and back muscles in our test is probably more comparable to treadmill exercise.[13]

In subjects able to perform both tests there were no statistically significant differences between the paired cardiovascular responses to the arm-crank and treadmill tests. Three of the 10 patients who had negative responses to both studies did not achieve 85

percent of their maximal predicted heart rate with arm-crank exercise. Achievement of this rate during treadmill exercise has been associated with a high degree of sensitivity in relation to coronary arterial obstruction.[3] However, two of these patients achieved higher double products with the arm-crank test. Since the double product is a reliable estimate of myocardial oxygen demand,[14,15] sensitivity of the arm-crank test was probably equal to that of the treadmill test in these two patients. When S–T segment changes were compared, the only difference between the two tests in our patients was that one patient with a negative arm-crank study had a false positive treadmill test. Thus, arm-crank exercise produced heart rate and blood pressure responses similar to those of treadmill exercise in our patients, and was equally as sensitive in detecting coronary artery disease.

We have demonstrated that arm-crank exercise can be accomplished by patients unable to perform leg exercise and that coronary artery disease can be detected by this method in such patients. Many of the nonambulatory patients with negative arm-crank studies did not reach 85 percent of their maximal predicted heart rate. The mean percent of the maximal predicted heart rate in these 20 patients was 73 percent. Nevertheless, because of higher blood pressures the mean double product achieved by these nonambulatory patients was not significantly different from that achieved by the ambulatory patients with negative arm-crank studies (22.4 ± 1.8 vs. 24.2 ± 1.0, $P > 0.1$). Therefore, the sensitivity of the arm-crank test in nonambulatory patients appears to be comparable to that observed in the ambulatory patients who had similar responses to arm-crank and treadmill exercise.

We have found the arm-crank test useful for evaluating chest pain and palpitation in patients unable to perform conventional leg exercise. Many of these patients are candidates for vascular and other types of surgery and the information obtained is helpful in their perioperative management. We have also used arm-crank ergometry to help elucidate chest pain induced exclusively by arm exercise in ambulatory patients. Presumably, this type of exercise would also be useful for assessing responses to drug therapy and physical rehabilitation programs.

In conclusion, we have demonstrated that a graded arm-crank exercise test is comparable to graded treadmill exercise in producing changes in heart rate and blood pressure sufficient to induce ischemic electrocardiographic changes in patients with coronary artery disease. In addition, we have shown the feasibility of utilizing this test to assess patients who are unable to perform leg exercise. Therefore, arm-crank ergometry is an excellent alternative to conventional treadmill exercise for evaluating suspected coronary artery disease in nonambulatory patients.

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Effects of Perhexiline on Symptomatic and Hemodynamic Responses to Exercise in Patients with Angina Pectoris

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The effects of perhexiline on symptomatic and hemodynamic responses to exercise stress were evaluated in 16 patients with coronary artery disease and angina pectoris. Exercise-induced angina was prevented (12 of 16) or delayed during perhexiline treatment and exercise heart rate decreased (117.4 ± 6.1 [standard error of the mean] to 105.3 ± 3.6 beats/min, $P < 0.05$). Ischemia-related indexes of left ventricular dysfunction were attenuated (stroke work index 70.9 ± 5.7 to 86.4 ± 5.3 g-m/beat per m^2 and filling pressure 26.4 ± 3.0 to 17.7 ± 2.5 mm Hg, $P < 0.01$) without evidence for depression of other indexes of ventricular function. Additionally, the exercise diastolic pressure-time index increased 36.5 ($P < 0.01$) and the diastolic pressure-time/tension-time ratio increased 38 percent ($P < 0.05$) with perhexiline in the patients who were free of angina. During increased exercise stress six patients achieved higher tension-time indexes before being limited by fatigue or dyspnea. The observed beneficial effects appear to be partly a result of reduced myocardial oxygen needs and improved oxygen supply.

Infusion of perhexiline (2-[2,2-dicyclohexylethyl] piperidine) produces coronary vasodilation and reduces heart rate in animals.[1,2] In normal subjects, this compound decreases the tachycardia induced by exercise.[3] These properties suggest that perhexiline, which is chemically unrelated to currently available antianginal agents, might be useful in patients with myocardial ischemia. Preliminary trials in patients with angina pectoris have generally shown improved exercise tolerance and a reduction in frequency and severity of anginal episodes.[4–6] Recently, data have been presented to suggest that perhexiline also has potent antiarrhythmic[7] and bronchodilator[8] actions that could be beneficial in patients with complicated angina. Furthermore, when the agent is administered orally, the duration of these effects has been long, apparently because perhexiline and its active derivatives are retained with lengthy biologic half-lives.[9] However, to date the potential clinical usefulness of perhexiline remains controversial,[10] and its hemodynamic effects have not been thoroughly examined.

An evaluation of the hemodynamic effects of perhexiline in patients with coronary artery disease complicated by angina pectoris constitutes the subject of this investigation. Because of the subjective nature of antianginal responses alone, emphasis is placed on the influence of perhexiline on ischemic ventricular performance during exercise. These actions are reviewed in terms of the effects observed with currently used antianginal agents.

Materials and Methods

Sixteen patients aged 43 to 67 years (mean 52 years) with stable angina pectoris and angiographically significant (greater than 75 percent obstruction) coronary artery disease comprised the study group (Table I). All pa-

From the Cardiopulmonary Branch, Internal Medicine Service and Clinical Investigation Service, U. S. Naval Hospital, Philadelphia, Pa. This study was supported by U. S. Navy Clinical Investigation Research Control Center, Project CICC 2-05-602. The opinions expressed herein are those of the authors and cannot be construed as reflecting the views of the Navy Department or of the Naval Service at large. Manuscript accepted February 6, 1974.

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TABLE I

Clinical and Angiographic Data

Case no.	Age (yr) & Sex	Previous MI	NYHA Class	Exercise Work Load (watts)	ECG	Coronary Angiography	Left Ventricular Angiography	Other
1	53M	No	III	20	+	3 vessel disease	Inferior hypokinesis	Atherosclerotic peripheral vascular disease
2	55M	No	II	50	+	LAD, LC_x	Normal	Mild hypertension
3	46M	Inferior	II	35	+	3 vessel disease	Inferior hypokinesis	Atherosclerotic peripheral vascular disease
4	57M	Subendo-cardial	II	25	+	LAD, LC_x	Normal	None
5	52M	No	III	20	+	3 vessel disease	Normal	SVBG occluded
6	58M	Inferior	III	30	+	3 vessel disease	Generalized hypokinesis	None
7	53M	No	II	75	−	RCA, LC_x	Normal	RBBB
8	55M	No	II	50	+	RCA, LC_x	Anterior hypokinesis	Obstructive lung disease
9	50M	Inferior	II	75	+	RCA, LC_x	Inferior hypokinesis	None
10	44M	No	II	100	−	LAD, LC_x	Normal	DM
11	42M	Inferior	III	125	−	RCA, LAD	Anterior akinesis	DM
12	46M	Antero-lateral	II	30	+	3 vessel disease	Anterior dyskinesis	None
13	57M	No	III	30	−	3 vessel disease	Anterior akinesis	Mild hypertension
14	67F	Anterior	III	20	+	3 vessel disease	Generalized hypokinesis	SVBG occluded
15	53M	No	III	25	+	3 vessel disease	Not performed	None
16	46M	No	II	75	+	LAD, LC_x	Normal	SVBG occluded

DM = diabetes mellitus; ECG = electrocardiogram; LAD = significant narrowing of left anterior descending coronary artery; LC_x = significant narrowing of left circumflex coronary artery; − = less than 1 mm ischemic S-T segment depression; MI = myocardial infarction; NYHA Class = New York Heart Association functional classification; + = S–T segment depression of 1 mm or more; RBBB = right bundle branch block; SVBG = saphenous vein bypass graft.

tients were in functional class II or III of the New York Heart Association classification and had no evidence for congestive heart failure or other forms of heart disease. Administration of other antianginal agents was stopped 1 week before the study, but nitroglycerin was permitted until the day of the study. Before the study, all subjects gave informed consent to participation in an antianginal drug investigation that included the procedures outlined herein. All catheterizations were performed without premedication with the patients in a fasting state, and all data reported were obtained before administration of angiographic contrast agents.

Procedures: A no. 7 Cournand type catheter was positioned in the main pulmonary artery by way of an antecubital vein. Systemic arterial pressure was measured with use of an 18G Teflon® catheter inserted percutaneously into a brachial artery and a Statham P23Db transducer. Heart rate and S–T segment depression were measured from electrocardiographic lead V_5. Cardiac output and pressure recordings were obtained according to methods described in detail previously.[11] The catheter was advanced to the pulmonary capillary wedge position where left ventricular filling pressure, as reflected in the mean pulmonary capillary wedge pressure, was recorded from a Statham P23Db transducer. Diastolic pressure-time index was calculated according to the method of Buckberg et al.[12] from the area under the diastolic systemic arterial pressure curve by subtracting from this value the mean pulmonary capillary

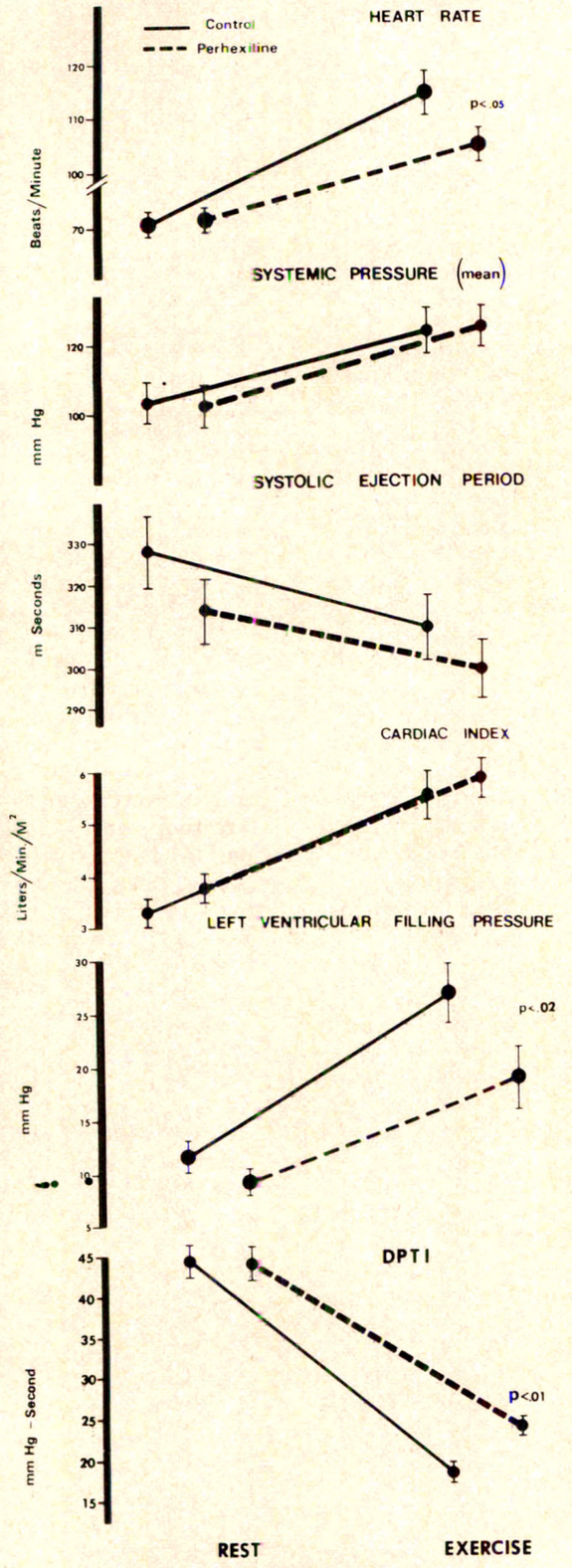

FIGURE 1. Summary of measurements at rest and during exercise before **(solid line)** and after **(dashed line)** perhexiline. Values represent means ± standard error of the means. DPTI = diastolic pressure-time index.

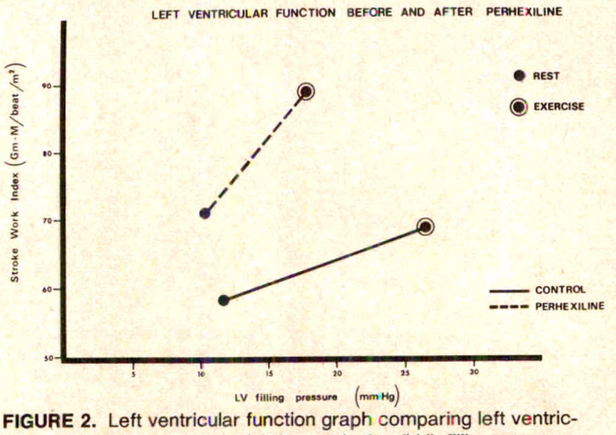

FIGURE 2. Left ventricular function graph comparing left ventricular stroke work index and left ventricular (LV) filling pressure from rest to exercise before and after perhexiline. Note the shift upward and to the left with perhexiline.

wedge pressure. These hemodynamic measurements were made at rest. Each patient then performed supine leg exercise on a bicycle ergometer (Collins) at a constant, individualized work load previously determined to evoke angina pectoris consistently after 3 to 5 minutes. The details of this exercise protocol and its ability to assess other antianginal interventions have been previously reported from our laboratory.[13,14] The pressure and cardiac output measurements were repeated during exercise-induced angina pectoris. All data were recorded on a multichannel photographic recorder at a speed of 25 mm/sec. Recording speeds of 200 mm/sec were used for the systolic ejection period and diastolic pressure-time index measurements and 10 mm/sec for cardiac output determinations.

After the initial study, the patients began taking perhexiline (200 mg orally, twice daily). After at least 10 days of therapy, they were restudied in an identical manner 4 hours after their morning dose. The exercise work load and duration were identical to those of the control test before administration of perhexiline, and data were collected at the same time during exercise. Patients not experiencing angina then continued exercise to the point of fatigue, or a maximum of 6 minutes. Results were analyzed statistically by the *t* test for paired data.

Follow-up studies: After completion of the restudy the patients were discharged from the hospital and followed up at biweekly intervals. During this period they took either perhexiline or placebo in a double-blind crossover study. All patients kept daily diaries and returned for reevaluation of exercise tolerance at monthly intervals, using the previously described protocol.

The following formulas were used: systolic ejection period (SEP) in seconds; cardiac index (CI) in liters/min per m^2 = cardiac output/body surface area; left ventricular stroke work index in g-m/beat per m^2 = CI/HR × (mean systolic pressure − mean pulmonary capillary wedge pressure) × 1.36/100; left ventricular work index in kg-m/min per m^2 = CI × (mean systolic pressure − mean pulmonary capillary wedge pressure) × 1.36/100; tension-time index (TTI) in mm Hg-sec/min = (mean systolic pressure) (HR)(SEP): diastolic pressure time index (DPTI) in mm Hg-sec; DPTI/TTI = (DPTI)(HR)/TTI: mean systolic ejection rate, in ml/sec per m^2 = CI/HR/SEP; systemic vascular resistance = mean systolic pressure/cardiac output in resistance units; pulmonary arteriolar resistance ≒ (mean

TABLE II

Hemodynamic Responses to Perhexiline During Exercise (means ± standard errors of the means)

State	HR	SPm	SEP	LVFP	CI	SWI	LVWI	MSER	DPTI	DPTI/TTI
					Angina-Free Group (12 patients)					
R	70.3 ± 3.7	102.2 ± 3.2	0.327 ± 0.011	11.6 ± 1.4	3.2 ± 0.35	60.1 ± 5.6	4.0 ± 0.5	142 ± 36	46.7 ± 4.4	17.6 ± 5.0
E	117.4 ± 6.1*‡	128.2 ± 3.6	0.307 ± 0.012	27.9 ± 4.1†‡	6.0 ± 0.68	76.9 ± 7.3	8.4 ± 1.1	183 ± 48	18.1 ± 1.6†	11.7 ± 3.7*
Rp	71.7 ± 3.7	102.2 ± 3.2	0.315 ± 0.011	8.7 ± 1.7	3.6 ± 0.41	68.4 ± 7.3	4.8 ± 0.66	160 ± 42	46.0 ± 5.0	16.7 ± 4.8
Ep	105.3 ± 3.6*‡	126.1 ± 3.1	0.300 ± 0.009	15.6 ± 2.4†‡	6.0 ± 0.53	89.1 ± 6.9	9.0 ± 0.84	202 ± 39	24.7 ± 1.6†	11.6 ± 3.6*
					Angina Group (4 patients)					
R	67.5 ± 4.8	100 ± 6.8	0.330 ± 0.158	11.3 ± 1.6	3.5 ± 0.52	61.6 ± 10.1	4.3 ± 0.79	160 ± 44	41.4 ± 4.7	15.9 ± 4.1
E	100.2 ± 7.0	113.2 ± 8.3	0.315 ± 0.005	23.5 ± 4.3	4.8 ± 0.36	58.8 ± 5.8*	5.9 ± 0.83*	162 ± 42	19.8 ± 2.8	13.4 ± 3.8
Rp	71.8 ± 3.7	106 ± 7.6	0.312 ± 0.118	10.0 ± 2.0	4.2 ± 0.24	75.2 ± 5.6	5.4 ± 0.50	186 ± 48	40.7 ± 1.8	14.6 ± 4.0
Ep	99.2 ± 7.2	122.7 ± 8.7	0.300 ± 0.015	21.7 ± 5.9	5.7 ± 0.38	81.1 ± 8.1	8.0 ± 1.2	191 ± 49	23.1 ± 0.8	12.2 ± 3.8

* = $P < 0.05$; † = $P < 0.01$ (before to after perhexiline); ‡ = $P < 0.05$; § = $P < 0.01$ (change during exercise, before perhexiline to after perhexiline).

CI = cardiac index (liters/min per m²); DPTI = diastolic pressure-time index (mm Hg sec); E = exercise; Ep = exercise after perhexiline; HR = heart rate (beats/min); LVFP = left ventricular filling pressure (mm Hg); LVWI = left ventricular work index (kg-m/beat per m²); MSER = mean sytolic ejection rate (cc/sec); R = rest; Rp = rest after perhexiline; SEP = systolic ejection period (sec); SPm = mean systemic arterial pressure (mm Hg); SWI = left ventricular stroke work index (g-m/beat per m²); TTI = tension-time index.

pulmonary arterial pressure − mean pulmonary capillary wedge pressure) cardiac output in resistance units.

Results

The hemodynamic data obtained at rest and during exercise before and after administration of perhexiline are summarized in Table I and Figures 1 and 2.

Fifteen of the 16 patients had angina during exercise before administration of perhexiline. In one patient exercise was terminated because 2 mm S–T segment depression occurred before development of chest pain.

Hemodynamic changes in all patients (Fig. 1): After administration of perhexiline, neither resting heart rate, mean systemic pressure, systolic ejection period, or their product changed significantly. Comparison of mean values during exercise (Fig. 1) demonstrated a smaller increase in heart rate (43.5 ± 4.0 [standard error of the mean] versus 32.1 ± 2.7 beats/min, $P < 0.004$) in all patients studied as the peak heart rate achieved was lessened during administration of perhexiline (113.1 ± 5.2 to 103.8 ± 3.2, $P < 0.05$); systemic pressure and systolic ejection period values were not significantly altered. Diastolic pressure-time index increased 29 percent ($P < 0.01$), whereas the diastolic pressure-time/tension-time ratio increased 36 percent ($P < 0.05$). The responses of left ventricular stroke work index and filling pressure during exercise before and after administration of perhexiline are summarized in Figure 2. The exercise stroke work index/filling pressure relation increased in all but one patient after treatment with perhexiline. During exercise, left ventricular stroke work index increased 22 percent ($P < 0.02$) and left ventricular filling pressure declined 49 percent ($P < 0.02$), thus indicating improved left ventricular performance. Neither pulmonary arteriolar nor systemic vascular resistance values were altered by administration of perhexiline.

Angina vs. angina-free group: According to their pain response to exercise at restudy, during treatment with perhexiline, the patients were classified into two groups (Table II). The angina group was composed of four subjects whose angina was not completely alleviated by administration of perhexiline. Exertional angina recurred in these four patients although it was less severe and delayed in two. The angina-free group consisted of the remaining 12 patients in whom perhexiline was completely effective in preventing effort angina. With perhexiline, these patients could perform work without angina for considerably longer periods than before treatment.

Differences are apparent between the groups, the angina-free patients achieving a greater heart rate (Table II) than the angina group during the control exercise period. Perhexiline modified peak heart rate achieved with identical exercise to a greater extent in the angina-free group (−10.3 percent, $P < 0.04$) than in the angina group (−1 percent, not significant); the mean peak heart rate and pressure reached by the angina-free patients was 105.3 beats/min and 126.1 mm Hg, respectively, compared with 117.4 beats/min and 128.2 mm Hg before treatment with perhexiline. The angina group achieved a heart rate of 99.2 beats/min and systemic pressure of 122.7 mm Hg compared with 100.2 beats/min and 113.2 mm Hg with exercise before treatment with perhexiline. Accordingly, tension-time index was lower (4,229 vs. 3,805 mm Hg sec/min) in the angina-free patients for an identical amount of exercise since the duration of systolic ejection did not increase. The exercise-related tension-

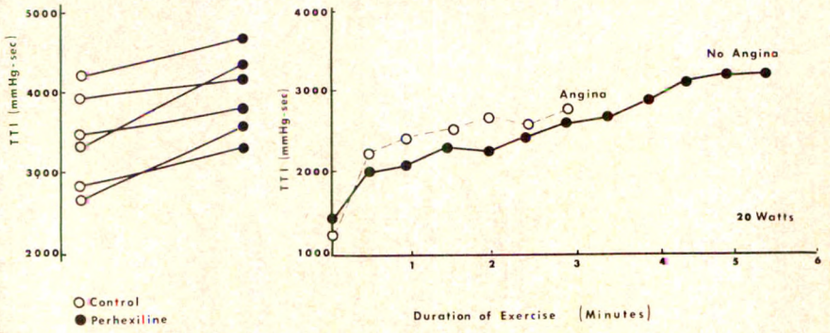

FIGURE 3. Effect of perhexiline administration on response of tension-time index (TTI) to exercise in six angina-free patients. **Left,** values during exercise-induced angina (O) and after perhexiline (●), when exercise was limited by fatigue. **Right,** effects of exercise on tension-time index before **(dotted line)** and after perhexiline **(solid line)** in a 53 year old patient whose response was typical of this group. With perhexiline he exercised for almost 3 additional minutes, achieving a higher tension-time index without angina before he was limited by fatigue.

time index increase declined 22 percent in the angina-free patients but only 7 percent in the angina group. This difference was significant ($P < 0.05$). The diastolic pressure-time index increased (18.1 ± 1.6 to 24.7 ± 1.6 mm Hg sec, $P < 0.01$) during exercise after perhexiline as the diastolic pressure-time/tension-time ratio increased 38 percent ($P < 0.05$) in the angina-free patients. By comparison, in the angina group diastolic pressure-time index and diastolic pressure-time/tension-time ratio showed nonsignificant changes of 16.7 and 10.5 percent, respectively, during exercise after treatment with perhexiline.

After these measurements made at the same intensity and duration of exercise, the angina-free patients continued to exercise for an average of 5.2 minutes, compared with 3.1 minutes before treatment with perhexiline. During this higher level of stress, six patients achieved greater tension-time indexes without experiencing angina than they reached before perhexiline (Fig. 3) as their effort was now limited by fatigue (four patients) or dyspnea (two patients).

Resting left ventricular filling pressure values were normal (13 mm Hg or less) in all but two patients, one in each group. Before treatment, a precipitous increase in left ventricular filling pressure was observed in each group during exercise at angina (from 11.6 to 27.9 mm Hg in angina-free patients and 11.3 to 23.5 mm Hg in the angina group) (Table II). After treatment with perhexiline, the angina-free patients had a more marked reduction (44 percent, $P < 0.04$) in left ventricular filling pressure at the same level of exercise than the angina group (7.8 percent decrease; not significant). The cardiac index increment during exercise, was not significantly altered by treatment with perhexiline in either group. Perhexiline caused no depression of left ventricular work index or mean systolic ejection rate during exercise (Table II).

No major side effects or complications occurred during this short-term trial or in relation to the investigational procedures. Early in the treatment period, two patients noted very mild, transient (1 to 2 days) lightheadedness unrelated to changes in blood pressure or pulse rate.

Follow-up results: Fourteen of the 16 patients reported less frequent episodes of angina and ability to perform more strenuous physical activity before angina was precipitated; 2 patients noted no change compared with placebo at this fixed dose. The average number of anginal episodes and the amount of nitroglycerin consumed per month were significantly ($P < 0.05$) reduced, from 46 ± 6 to 19.8 ± 6.0 episodes/month and 27 ± 3 to 9 ± 2.0 tablets/month, respectively. Serial resting 12 lead electrocardiograms were unchanged when compared with those taken at the initial evaluation before treatment with perhexiline, and no history indicating that myocardial infarction had occurred between the two studies was obtained. Perhexiline significantly ($P < 0.01$) prolonged the duration of exercise (301 ± 18 seconds) compared with the change after placebo (212 ± 20 seconds) as peak heart rate was reduced.

Discussion

Our results with orally administered perhexiline, in doses well tolerated by patients with coronary artery disease, are in agreement with those of preliminary studies[4–6] and support the evidence that perhexiline increases exercise tolerance of patients limited by angina pectoris. Increased effort tolerance was associated with a reduction in heart rate during identical levels of exercise of approximately 10 percent in the patients who were angina-free after treatment with perhexiline. This change was not offset by changes in the response of arterial blood pressure or the duration of systole. Thus, perhexiline reduces the myocardial oxygen cost of a given level of exercise.

Perhexiline and ventricular performance during exercise: That perhexiline alters ischemic left ventricular function is indicated by prevention of the precipitous abnormal increases in left ventricular filling pressure observed during exercise. Left ventricular dysfunction was reduced, as evidenced by a shift to the left and upward of the stroke work/filling pressure relation (Fig. 2). By contrast, patients without relief of angina had increases in heart rate and left ventricular filling pressure with exercise during perhexiline therapy similar to those of the control exercise period (Table II). These results also added objective confirmation of the ability of perhexiline to alter or prevent myocardial ischemia. The finding that the tension-time index increased significantly in six of the angina-free patients during increased exercise stress may represent an increase in myocardial oxygen consumption during perhexiline therapy (Fig. 3). Within the limitations of this index, as emphasized by others,[15] these results can be interpreted to indicate that perhexiline enhances myocardial oxygen delivery in some patients with coronary artery disease.

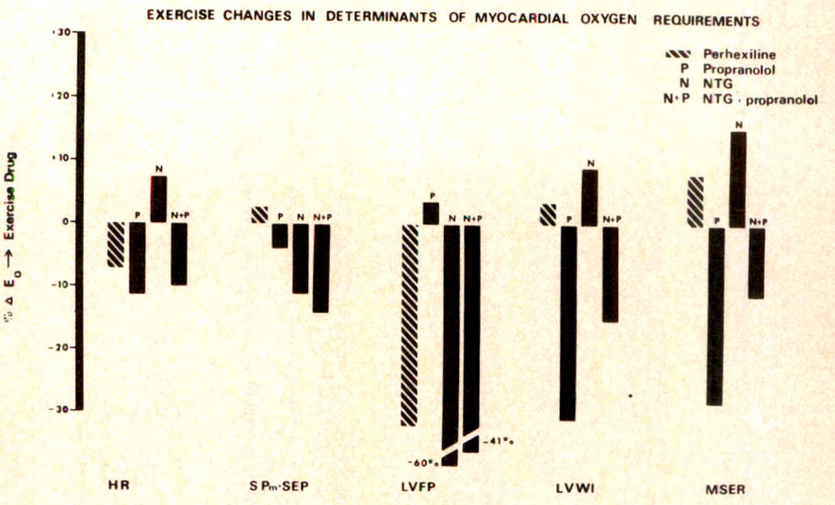

FIGURE 4. Comparison of the effects of perhexiline **(striped bars)**, propranolol (P), nitroglycerin (N) and nitroglycerin and propranolol (N + P) on several hemodynamic determinants of myocardial oxygen consumption. The percent difference during exercise (pre to post drug administration) for each function is indicated on the vertical axis. Abbreviations on the horizontal axis are the same as in Table II. Note that perhexiline has actions that resemble those of propranolol (reduction of exercise heart rate) and nitroglycerin (enhanced left ventricular work index and reduced left ventricular filling pressure) without undesirable oxygen-wasting effects (increased left ventricular filling pressure with propranolol and increased heart rate with nitroglycerin).

In spite of the assumptions involved in this index, support for the latter suggestion was observed through the increase in a major determinant of myocardial blood supply, namely the diastolic pressure-time index.

Others[12,16] have shown that changes in ventricular performance and myocardial blood flow distribution can be predicted by using a ratio of the diastolic pressure-time index (to estimate subendocardial flow) and the tension-time index (to estimate cardiac oxygen needs). Exercise produces tachycardia and enhances contractility increasing myocardial oxygen requirements; at the same time, although systemic pressure increases, diastole is shortened. In patients with coronary artery disease left ventricular diastolic pressure also increases and these needs are only partially met by increased coronary blood flow resulting from coronary vasodilatation. The net effect limits the potential increase in flow produced by a given degree of coronary dilatation making it inadequate to meet simultaneously increasing oxygen requirements. At this time subendocardial flow is dependent on the relation between diastolic coronary-left ventricular pressure gradients and the time available for perfusion (diastolic pressure-time index). In our study diastolic pressure-time shortened critically with exercise stress but was increased during exercise after perhexiline therapy. A significant increase also occurred in the diastolic pressure-time/tension-time ratio after administration of perhexiline during exercise. These changes imply an increase in subendocardial blood flow relative to oxygen requirements and suggest an additional explanation for the prevention of angina and impaired ventricular performance during stress after perhexiline therapy.

Direct cardiac effects of perhexiline: Evidence for both direct and extracardiac effects of perhexiline has been derived from previous studies in laboratory animals using direct infusion of perhexiline. Hudak et al.[1] demonstrated large decreases in coronary, pulmonary and systemic vascular resistance and heart rate after administration of 1 and 3 mg/kg body weight in anesthetized dogs. Reflex vasoconstriction and tachycardia did not occur. In these studies perhexiline did not alter the heart rate effects of isoproterenol, and propranolol did not affect the changes in arterial pressure or coronary flow that followed treatment with perhexiline. Bilateral vagotomy did not modify either the hypotension or negative chronotropic actions of perhexiline. Directionally similar but quantitatively less reduction in coronary and systemic resistances was reported by Cho et al.[2] at low and high perfusion rates in a right heart bypass preparation. They also observed a fall in cardiac rate, work and oxygen consumption. The heart rate effect was not altered by vagotonic, cholinergic or adrenergic blockade.[17]

In acute studies in six unanesthetized patients with severe coronary atherosclerosis and angina pectoris, Rowe et al.[18] noted a significant decline in resting heart rate after a 40 to 60 mg right heart infusion over 3 to 5 minutes. No change was noted in mean systemic blood pressure. Cardiac output also decreased with associated reduction of left ventricular work, whereas mean pulmonary arterial pressure was unchanged. These workers suggested that the effect of perhexiline was related to dose and route of administration. Hemodynamic measurements during exercise have not been reported.

In our study orally administered perhexiline did not induce systemic arterial hypotension or significant decreases in peripheral resistance, yet its cardiac action persisted. No evidence for reduced cardiac work as suggested by prior studies was demonstrated. It is likely that the observed responses in our unanesthetized patients after treatment with perhexiline are more complex than merely direct vascular effects because of each vascular bed's intact autoregulatory capacity. The sensitivity to perhexiline of dog heart muscle and peripheral vessels probably differs from that of man. In addition, the effects of perhexiline on hemodynamic variables may be different during its continued absorption from the gastrointestinal tract than after bolus intracardiac infusion. Considering this compound's long excretion half-life[9] the tissue level of the drug must be very different after days of

continuous oral administration from the level during bolus injection studies.

Mechanism of antianginal and hemodynamic effects of perhexiline: Perhexiline-induced changes in cardiac function differ from responses described with other antianginal agents. Data previously reported[14] from similar studies conducted in our laboratory after nitroglycerin, propranolol and their combination are compared with perhexiline in Figure 4. Nitroglycerin decreases left ventricular filling pressure during exercise but also reduces cardiac output, ejection time and systemic pressure, acting to diminish oxygen requirements. However, baroreceptor-mediated increases in heart rate and contractility tend to have opposite effects on myocardial oxygen consumption. Improved left ventricular function during exercise (increased stroke work index/left ventricular filling pressure ratio) with administration of perhexiline resembles responses observed with nitroglycerin but without decreased coronary filling pressure or the additional oxygen costs of reflex tachycardia.

Although perhexiline is not a beta adrenergic blocking agent,[1] the reduction in exercise-induced tachycardia is similar to that observed with propranolol. However, cardiac output and ejection rate also decline as the duration of systole is prolonged after propranolol with equivalent abnormal increases in left ventricular filling pressure during exercise.[14] Perhexiline has the beneficial oxygen-sparing effect of propranolol with respect to alteration of exercise heart rate, without its undesirable myocardial depression (decreased stroke work index/left ventricular filling pressure). The hemodynamic response during treatment with perhexiline more closely resembles that observed with use of both nitroglycerin and propranolol. This combination favorably alters left ventricular function during exercise by increasing stroke work while reducing left ventricular filling pressure.[14] Blockade of reflex-mediated increases in heart rate and contractility lessens oxygen requirements. Accordingly, perhexiline affords very similar ventricular functional responses while some persisting, less desirable properties (depressed left ventricular work and mean systolic ejection rate) of the former drug combination are absent.

Conclusion

The purpose of this study was to assess whether orally administered perhexiline has a measurable influence on clinical and hemodynamic responses to exercise in patients with angina pectoris. Our data clearly support the initial findings of others that this drug is of value in preventing effort-induced angina pectoris. This beneficial effect, persisting 4 hours after administration, relates to hemodynamic actions that include reduced exercise tachycardia, prolongation of the diastolic pressure-time interval and reduction of ischemia-related left ventricular dysfunction. Although the exact mechanism of the antianginal and hemodynamic actions of perhexiline has not been determined, our study provides indirect support that such responses result from a primary cardiac effect, possibly related to enhanced myocardial oxygen delivery. The improvement observed suggests that perhexiline is a useful addition to available means for prophylaxis of angina pectoris.

Acknowledgment

We thank Dr. William J. Hudak of Merrell-National Laboratories, Cincinnati, Ohio for kindly supplying the perhexiline and placebo used in this study. We are also grateful to Mrs. Kathy Dennish, who provided valuable assistance throughout this investigation.

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Myocardial Infarction After Exercise-Induced Electrocardiographic Changes in a Patient with Variant Angina Pectoris

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The electrocardiographic response to stress testing varies considerably in patients with variant angina pectoris: no change in the S–T segment as well as S–T segment depression and elevation have been observed. This report describes a patient with a resting ST–T abnormality that reverted to normal appearance with exercise. However, the patient experienced severe chest pain shortly after discontinuing exercise testing, and an electrocardiogram showed evidence of acute anterolateral infarction. The possible implications of such electrocardiographic changes are discussed.

Since Prinzmetal's preliminary report[1] in 1959 on a group of patients with a variant form of angina pectoris, much interest has been generated in methods of diagnosing this lesion. The early papers reported that chest pain and its associated electrocardiographic changes occurred primarily at rest or with ordinary exercise. In Prinzmetal's original study,[1] exercise testing (Master two-step technique) failed to provoke pain or the characteristic S–T segment elevation noted in these patients during spontaneously occurring chest pain. Either there was no S–T deviation with exercise, or S–T depression appeared. Since S–T segment depression after exercise also occurs in patients with the classic form of angina pectoris and in some with asymptomatic coronary artery disease, exercise tests have been thought to be of little value in diagnosing the variant form of angina. More recently Kemp[2] described a patient with variant angina who manifested intermittent S–T segment elevation with treadmill stress testing, and suggested that such testing may be a diagnostic aid in cases of variant angina.

This report presents a patient with atypical chest pain and resting electrocardiographic abnormalities that reverted to normal appearance with exercise. However, evidence of acute myocardial infarction developed shortly after stress testing was discontinued.

Case Report

A 61 year old white male postmaster was referred for evaluation of chest pain he had experienced for approximately 3 months before admission. The pain, located in the left precordium, was characterized as "squeezing." It generally occurred at rest and was not precipitated or aggravated by exercise, emotional upset or sexual intercourse. The patient stated that he was an avid bird hunter and could follow his dogs for 5 to 6 miles a day in cold weather without pain or undue shortness of breath. He denied orthopnea, paroxysmal nocturnal dyspnea, dependent edema or palpitations. He stated that the pain occurred four to five times a day, never lasted longer than 30 minutes and was generally relieved by nitroglycerin in 3 to 4 minutes. He had received intermittent treatment for hypertension for approximately 25 years and also borderline diabetes, treated by diet alone. He had smoked one pack of cigarettes a day for approximately 40 years and denied excessive alcohol intake. He had no known lipid abnormalities and no history of gouty arthritis. There was no premature coronary artery disease or diabetes in his immediate family

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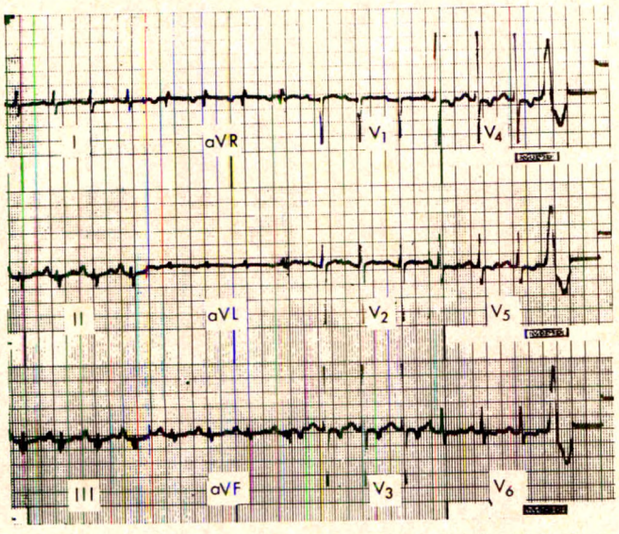

FIGURE 1. Standard 12 lead electrocardiogram obtained before exercise testing (paper speed 25 mm/sec).

but two siblings had hypertension, one sustaining a cerebrovascular accident. Medications at the time of admission included methyldopa and amitriptyline.

Physical examination revealed a tall, rather obese white man with a blood pressure of 180/105 mm Hg in both arms; heart rate was 76 beats/min and regular. Funduscopic examination revealed moderate arteriolar narrowing and arteriovenous nicking without hemorrhages, exudates or microaneurysms. He had no visible xanthomas or arcus senilis. Cardiovascular examination was entirely normal except for the auscultatory finding of a fourth sound gallop.

Initial chest roentgenograms with cardiac fluoroscopy revealed a normal cardiothoracic ratio without specific chamber enlargement. There was a small area of calcification in the region of the left anterior descending coronary artery. The admission electrocardiogram revealed a sinus rhythm with a normal QRS axis, slightly depressed S–T segments and T wave inversion in leads V_4 through V_6 (Fig. 1). QRS voltage did not fulfill the criterion for left ventricular hypertrophy. Admission laboratory data included normal values for hematocrit, blood urea nitrogen and serum electrolytes. Uric acid was slightly increased (9.4 mg/100 ml). Results of fasting and 2 hour postprandial blood sugar determinations were normal. Serum cholesterol was 198 and triglyceride 117 mg/100 ml.

During the first two days the patient had no spontaneous episodes of chest pain. On the third hospital day he was subjected to a graded exercise test[3] (Sheffield-Reeves) using the stages of Bruce and McDonough.[4] Medications at that time included methyldopa, 250 mg four times a day, and hydrochlorothiazide, 50 mg once daily. In a fasting state with normal serum potassium, he achieved a maximal heart rate of 170 beats/min after 10 minutes and 30 seconds on the treadmill. This response was above that predicted for his age and prior activity level using the criteria of Bruce to assess functional aerobic capacity with the multistage treadmill test. The patient experienced no chest discomfort, nausea or undue leg discomfort. The previously described ST–T changes present at rest normalized with exercise; the S–T segment became isoelectric and the T wave reverted to a normal upright appearance (Fig. 2).

Approximately 10 minutes after discontinuation of stress testing, while still in the exercise laboratory, he began to experience nausea, vomiting and diaphoresis followed by left anterior precordial pain that was increasingly severe and prolonged. Repeated electrocardiograms revealed S–T segment elevation extending from leads V_2 through V_6; serial tracings and serum enzyme determinations confirmed the presence of an extensive anterolateral myocardial infarction (Fig. 3). His hospital course was complicated by recurrent arrhythmias and persistence of S–T segment eleva-

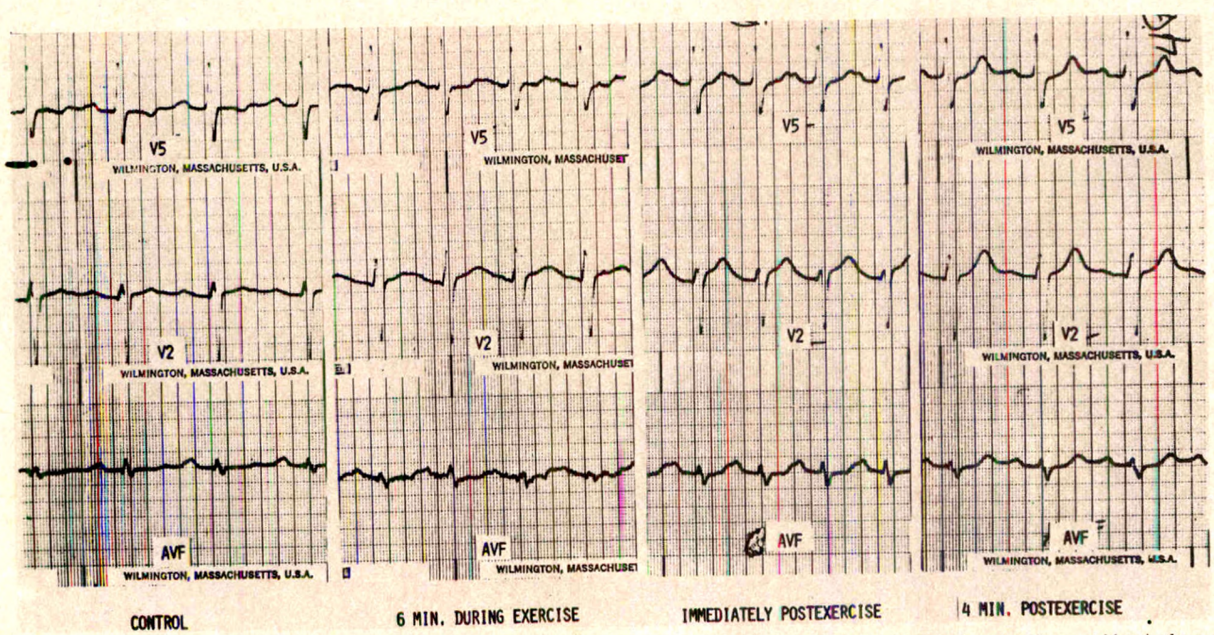

FIGURE 2. Representative sections of exercise monitoring leads (V_5, V_2 and aVF) obtained with the patient in the standing position before exercise, during the 6th minute of exercise, immediately after and 4 minutes after exercise (paper speed 50 mm/sec).

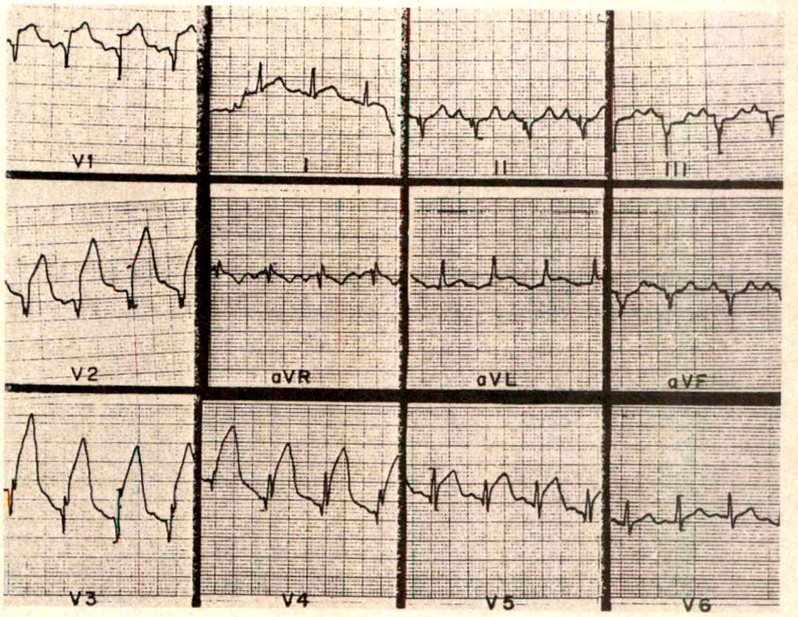

FIGURE 3. Standard 12 lead electrocardiogram obtained after the onset of chest pain 20 minutes after exercise (paper speed 25 mm/sec).

tion (Fig. 4). Subsequent evidence of paradoxic pulsation was found on physical and fluoroscopic examination. He was subsequently discharged symptom-free on the 32nd day after infarction.

During the 6 months after discharge the pattern of his chest pain has changed; it is now usually precipitated by exertion of only one to two blocks of walking. Cardiac catheterization was performed 10 months after infarction. Left ventricular biplane angiograms revealed ventricular enlargement with anterior wall akinesis. Coronary angiograms revealed proximal occlusion of the left anterior descending artery just distal to the first septal branch. The right coronary artery was dominant and showed a 90 percent stenosis in its proximal third and a good distal vessel. The left main and circumflex arteries were free of detectable lesions.

Discussion

As in the case presented by Kemp,[2] a resting electrocardiogram could not be obtained during an episode of pain. However, the quality, location, periodicity, lack of precipitation with exercise and response to nitroglycerin were such that a diagnosis of variant angina pectoris seems most appropriate.

As with Kemp's patient and those previously presented by Prinzmetal et al.[1] there was a total absence of chest pain during vigorous exertion. Thus, if treadmill testing is to be used in the diagnosis of variant angina, one must rely heavily on interpretation of ST–T changes since subjective symptoms will proba-

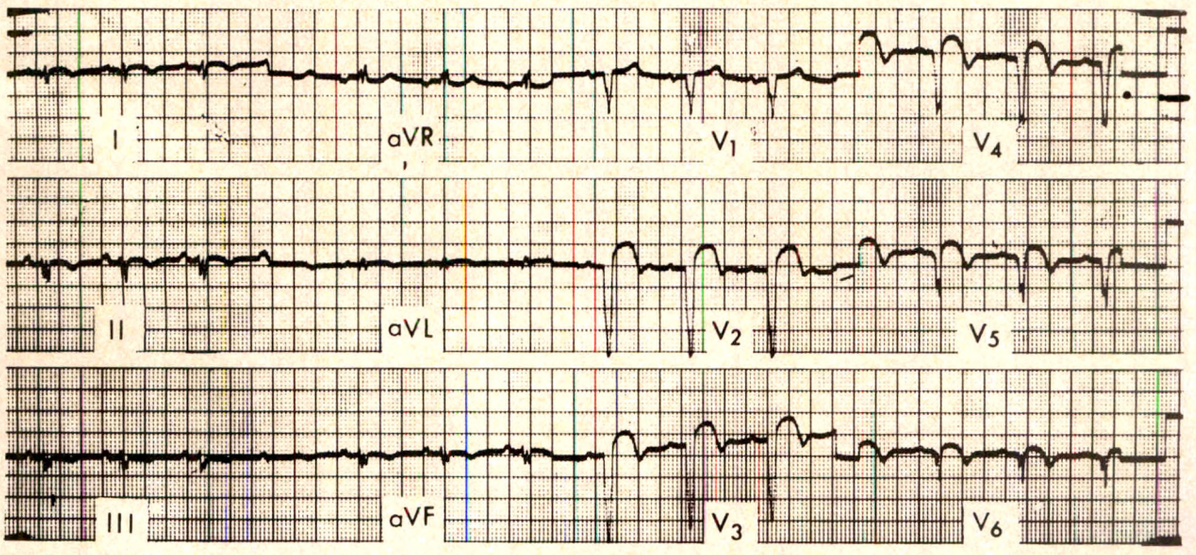

FIGURE 4. Standard 12 lead electrocardiogram obtained 17 days after myocardial infarction, revealing persistent S–T segment elevation (paper speed 25 mm/sec).

bly be absent. At this point considerable difficulty is encountered. The conversion of a normal control tracing to one showing an ischemic S–T segment in response to stress testing is not specific for myocardial hypoxia and may be produced by left ventricular hypertrophy, left ventricular overload without detectable hypertrophy, intraventricular conduction defects, digitalis glycosides as well as hyperventilation.[3,5] The standard criteria are based on S–T segment depression (from a previous isoelectric S–T segment) initiated by J point depression of 0.1 mv or more and followed by an S–T segment that is flat or downsloping (slope of less than +1 mv/sec).[3] S–T segment elevation with exercise has also been shown to occur in patients with significant coronary artery disease. In the study by Fortuin and Friesinger,[6] 11 of 12 patients with exercise-induced S–T segment elevation were found at coronary angiographic examination to have total or near total occlusion of a major coronary artery. Manvi and Ellestad[7] recently reported data on patients with a ventricular aneurysm and a normal S–T segment at rest who subsequently manifested S–T segment elevation during maximal treadmill testing. Their patients were found to have large apical aneurysms with major obstruction in the left anterior descending coronary artery. Kemp's patient with variant angina also demonstrated S–T segment elevation with treadmill testing, and angiographic studies revealed severe stenosis of both the proximal circumflex (98 percent) and proximal left anterior descending (90 percent) coronary arteries.

Hence, in patients with isoelectric S–T segments at rest, it has been shown that either significant S–T segment depression or elevation with exercise correlates highly with significant coronary artery disease.[6,8,9] In patients with S–T segment abnormalities at rest, interpretation becomes difficult.[10] In patients with typical angina pectoris, the subjective sensation of typical chest pain with exertion can be used as an end point for terminating stress testing. However, in patients with variant angina, pain may be absent throughout the testing period. To compound the problem further, Prinzmetal et al., in their original papers,[1,11] noted that patients with resting electrocardiographic abnormalities may show apparent reduction of these changes during pain. Although others[12] have noted both normalization of a previously depressed S–T segment to the base line and the associated return of an inverted T wave to an upright position, these changes have not been assessed in detail. In our patient, such changes were the harbingers of later frank S–T segment elevation indicating extensive myocardial infarction.

Clinical Implications

Exercise testing is being used more extensively for both diagnostic and prognostic evaluation of patients. Patients with atypical chest pain are particularly likely to undergo such testing. A recent survey of 73 medical centers performing such evaluation indicates that these procedures are safe in most patients when properly administered (mortality 1/10,000 tests or 0.01 percent; morbidity 2.4/10,000 tests or 0.02 percent).[13] However, patients with atypical chest pain revealed by careful questioning to have probable variant angina may be at particularly high risk for maximal or submaximal stress testing. We believe the following considerations should be kept in mind when evaluating such patients:

1. Chest pain, a critical signal for terminating stress testing, is absent in the majority of these patients despite markedly increased myocardial oxygen demands at maximal or near maximal treadmill testing.
2. S–T segment changes, which must be relied upon as an index of ischemia in the absence of pain, are unpredictable in this group of patients.
3. Normalization of previously abnormal ST–T changes during exercise may indicate progressive ischemia, as illustrated in our case, and may offer a false sense of security to the unsuspecting.
4. Since the pain most frequently occurs at rest or during ordinary exertion or at night, a more physiologic and less hazardous approach would be the use of continuous Holter monitoring to demonstrate the typical S–T segment changes that occur during these periods.[14]
5. Because of the grave prognosis that has been demonstrated in this group[15] and because of the previously mentioned difficulties inherent in some of the usual diagnostic procedures, it would seem advisable to proceed to early angiographic studies in an attempt to obtain a more definitive diagnosis. This procedure may be particularly useful not only in defining static areas of obstruction, but also in demonstrating coronary arterial spasm, as found by Dhurandhar et al.[16] during an episode of pain. This finding is of particular interest in light of Prinzmetal's original hypothesis that arterial spasm is the possible cause of pain in this group of patients.

Acknowledgment

We are grateful to Drs. T. Joseph Reeves, William P. Hood and George K. Massing for their editorial assistance and to Mrs. Liza Sipe and Florence Driskill for their assistance in the preparation of this manuscript.

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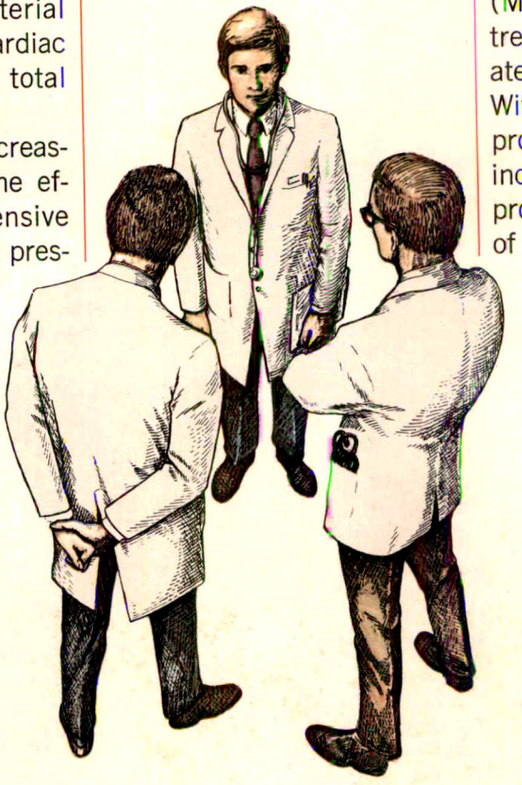

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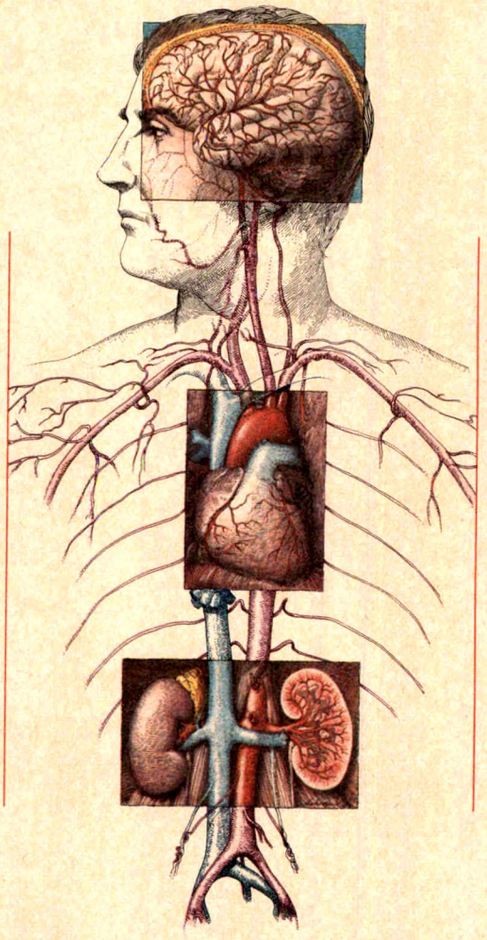

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Warnings: Acquired hemolytic anemia has occurred rarely in association with therapy with methyldopa. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of the anemia. Rarely, however, fatalities have occurred.

Some patients on continued therapy with methyldopa develop a positive direct Coombs test; incidence reported has averaged between 10% and 20%. It rarely occurs in first six months of therapy, and if not seen within twelve months, is unlikely to develop with continued administration. Positive Coombs test is dose-related; lowest incidence occurs in patients on 1 g methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa. Prior knowledge of a positive Coombs reaction aids in evaluation of cross match for transfusions. Patients with positive Coombs tests at time of cross match may exhibit incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with blood otherwise compatible in the major cross match may be carried out. If positive, advisability of transfusion with blood compatible in major cross match should be determined by hematologist or expert in transfusion problems.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy in several patients with liver dysfunction has shown microscopic focal necrosis compatible with drug hypersensitivity. Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen; reversible agranulocytosis has been reported. Methyldopa may interfere with measurement of creatinine by alkaline picrate method and of uric acid by phosphotungstate method. When used with other antihypertensive drugs, potentiation of antihypertensive action may occur.

Usage in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Perform periodic hepatic function tests and white cell and differential blood counts during first six to twelve weeks of therapy or in unexplained fever. Discontinue if fever, abnormalities in liver function tests, or jaundice appears. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Discontinue drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Anesthetics requirements may be reduced; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension may occur after dialysis because methyldopa is removed by this procedure.

Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Do not exceed recommended daily dose of 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure, including dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency, are seen occasionally. Angina pectoris may be aggravated. Symptoms of orthostatic and exercise hypotension may occur; if symptoms occur, reduce dosage. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distension, constipation, flatus, and diarrhea occur occasionally; these can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently; if edema progresses or signs of pulmonary congestion appear, discontinue drug. Rarely, urine exposed to air may darken due to breakdown of methyldopa or its metabolites. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression, reversible thrombocytopenia, drug-related fever and abnormal liver function studies with jaundice and hepatocellular damage (see **Warnings** and **Precautions**), rise in BUN, and a single case of bilateral Bell's palsy.

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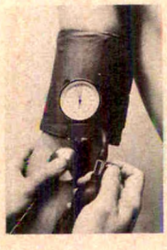
Family physicians are being urged to take blood pressure readings as a matter of office routine, regardless of the presenting complaint or the reason for the visit. And because many people do not see a family physician for relatively long periods of time, some experts are suggesting that ophthalmologists, gynecologists, dermatologists, orthopedists, psychiatrists, dentists, school nurses, family planning counselors, and other health-care personnel make blood pressure reading a routine part of every examination or consultation.

Of course, a diagnosis of hypertension cannot be made on the basis of a single reading, but routine blood pressure readings can uncover potential trouble in a certain proportion of patients. And when trouble is suggested, further evaluation can be pursued more effectively.



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THE AMERICAN JOURNAL OF CARDIOLOGY,® Official Journal of the American College of Cardiology, June, 1974, Vol 33, No. 7.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except May and October, semimonthly, by the Magazine Division, DUN-DONNELLEY PUBLISHING CORPORATION, a member of the Dun and Bradstreet Group. William F. Ward, Jr., President; John K. Abely, Vice President and General Manager, Magazine Division. EXECUTIVE, EDITORIAL AND ADVERTISING OFFICES: 666 Fifth Ave., New York, N.Y. 10019. Printed in Easton, Pennsylvania.

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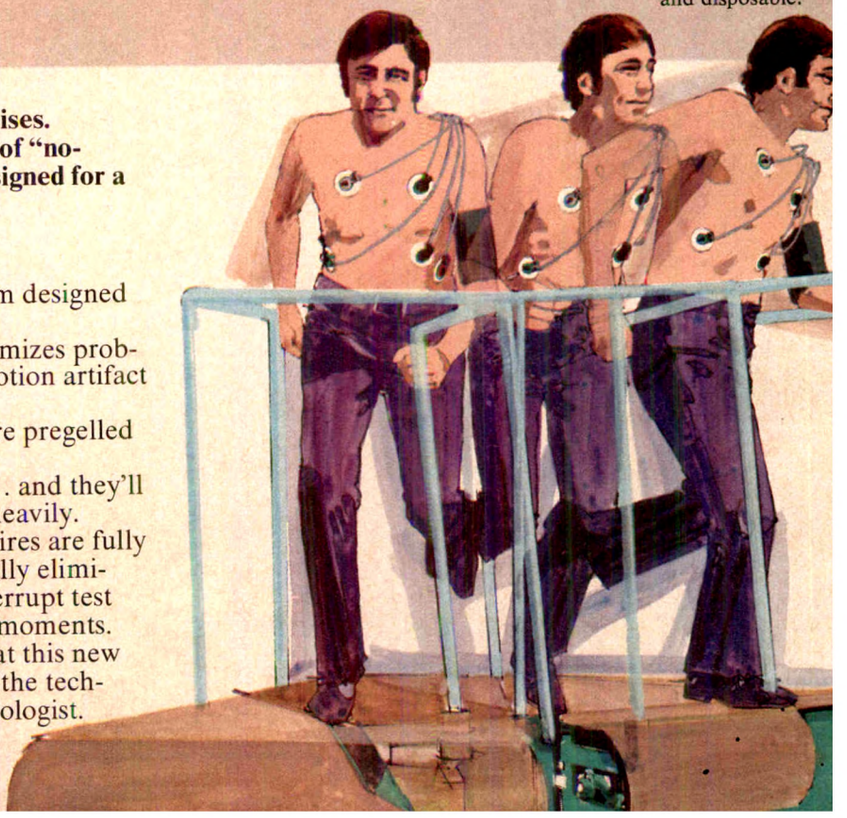

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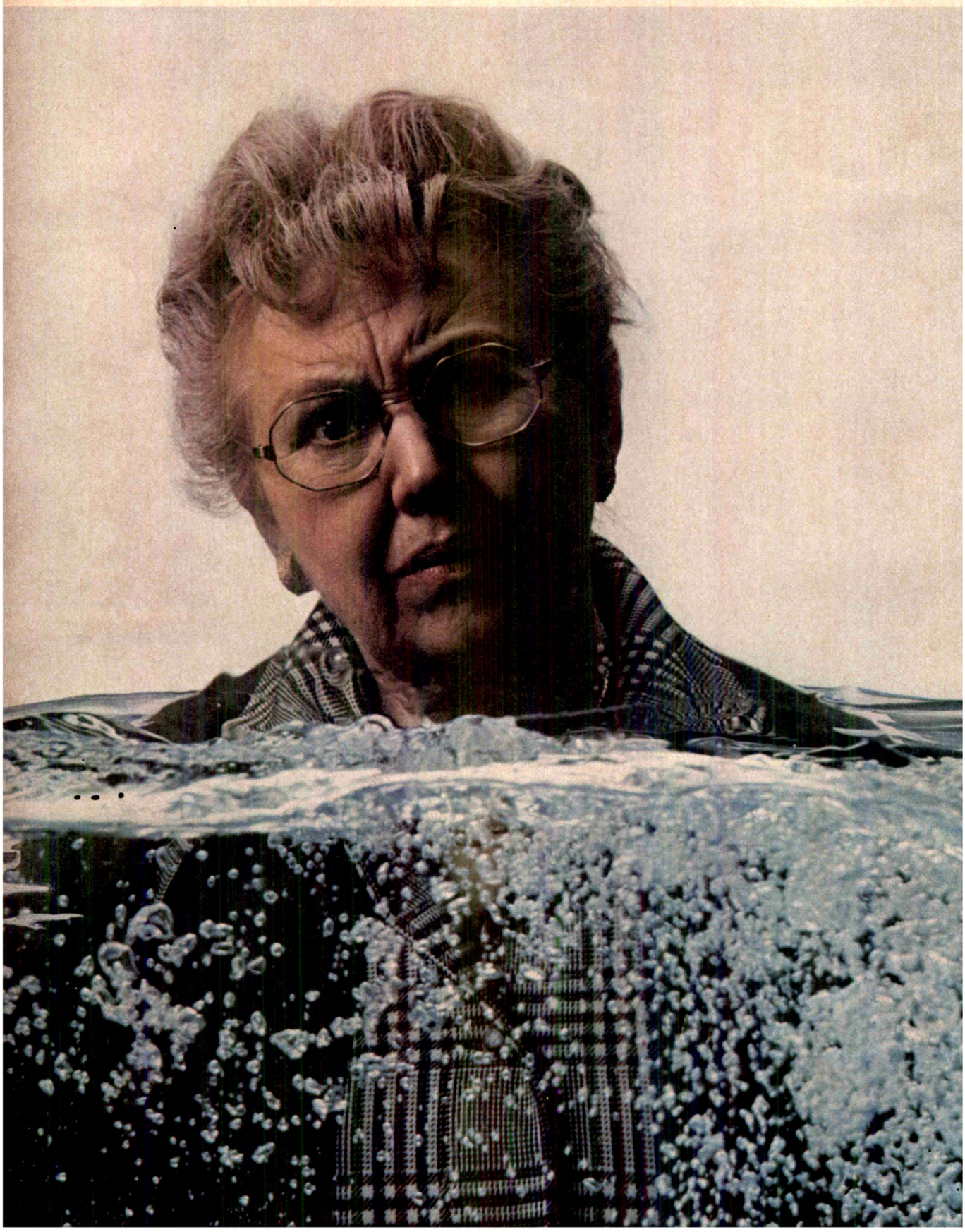

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CLINICAL STUDIES

819 Hemodynamic Effects of Noninvasive Systolic Unloading (Nitroprusside) and Diastolic Augmentation (External Counterpulsation) in Patients with Acute Myocardial Infarction

WILLIAM W. PARMLEY, KANU CHATTERJEE, YZHAR CHARUZI and H. J. C. SWAN

This study demonstrates the feasibility of combining noninvasive external counterpulsation and systolic unloading with infusion of nitroprusside to produce hemodynamic improvement in patients with acute myocardial infarction. The results of this combined therapy were better than those of either treatment alone in that counterpulsation reversed the decrease in diastolic blood pressure produced by nitroprusside and further increased the cardiac index.

826 Prognostic Indexes in Acute Myocardial Infarction Complicated by Shock

ABDELMONEM A. AFIFI, POTTER C. CHANG, VINNIE Y. LIU, PROTASIO L. da LUZ, MAX HARRY WEIL and HERBERT SHUBIN

Arterial blood lactate was the most reliable variable individually and in combination with other variables in assessing prognosis in 29 patients with acute myocardial infarction and shock. Blood flow measurements were more reliable than blood pressure measurements. Prognostic indexes like those discussed in this article provide an objective assessment of the severity of the patient's illness and his response to treatment.

833 Mechanism and Significance of Widened QRS Complexes During Complete Atrioventricular Block in Acute Inferior Myocardial Infarction

K. I. LIE, HEIN J. WELLONS, REINIER M. SCHUILENBURG and DIRK DURRER

Widened QRS complexes with a left bundle branch block configuration in patients with acute inferior wall myocardial infarction may be due to an atrioventricular (A–V) junctional escape rhythm with phase 4 left bundle branch block. Alternatively, in association with a right bundle branch block configuration they may represent a ventricular or fascicular escape rhythm. Widened QRS complexes during complete A–V block in acute inferior myocardial infarction have no prognostic significance.

840 Platelet Survival in Patients with Prosthetic Heart Vaves

R. KENNETH STUART, JOHN W. McDONALD, SURAJ P. AHUJA and JOHN C. COLES

These chromium-51 platelet survival studies in 20 patients with a prosthetic heart valve suggest that reduced platelet survival time was a result of damage to the prosthesis rather than of thrombus formation on the prosthesis. Only 1 of 10 patients with a prosthetic mitral valve and 4 of 10 patients with an aortic prosthesis had a significantly shortened platelet survival time.

Continued on page A13

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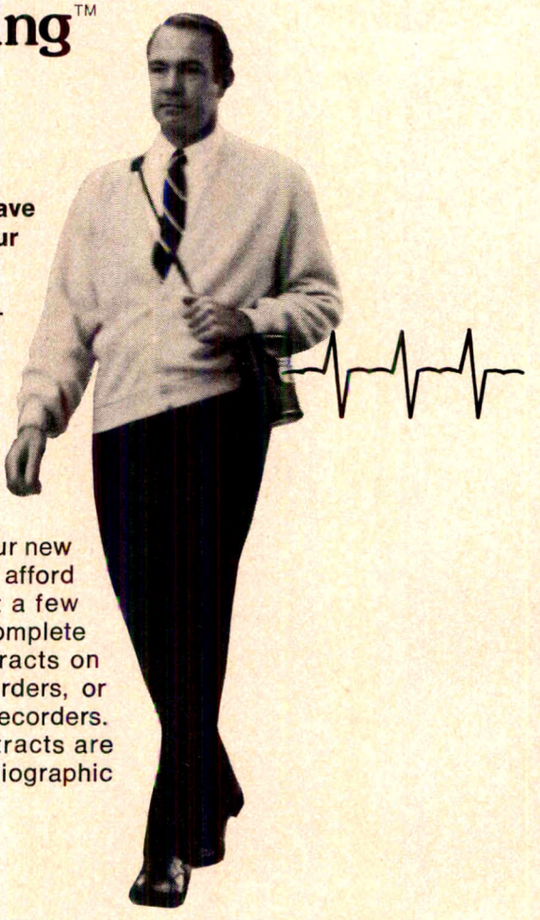

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EXPERIMENTAL STUDIES

845 Encephalogenic Cardiomyopathy After Stimulation of the Brain Stem in Monkeys

HSING I. CHEN, SHIH CHIEN SUN, CHOK YUNG CHAI, SHIH LIANG KAU and CHIEN KOU

Repeated electrical stimulation of the hypothalamus, pons and medulla in monkeys produced an increase in arterial blood pressure, cardiac arrhythmias, S–T or T wave changes in the electrocardiogram and ultrastructural damage to the myocardium. The myocardial lesions are attributed to activation of the sympathetic mechanism in the brain stem.

853 Reflex Inhibitory Effects of Vagal Afferents in Experimental Myocardial Infarction

PAUL KEZDI, R. KARL KORDENAT and SARDA N. MISRA

After injection of mercury into the circumflex coronary artery of closed chest anesthetized dogs not only did cardiac output, mean blood pressure and aortic nerve activity decrease as expected, but also postganglionic sympathetic nerve activity decreased unexpectedly, probably because of a powerful cardiac vagal afferent reflex. Cutting or blocking the vagus nerves immediately increased sympathetic nerve activity and then cardiac output, mean systemic blood pressure and aortic nerve activity in these animals.

861 Accumulation of Gallium-67 in Regions of Acute Myocardial Infarction

ROBERT J. KRAMER, ROBERT E. GOLDSTEIN, JOHN W. HIRSHFELD, Jr., WILLIAM C. ROBERTS, GERALD S. JOHNSTON and STEPHEN E. EPSTEIN

Radionuclide gallium-67 injected intravenously in eight dogs after ligation of the left anterior descending artery was found to accumulate preferentially in regions of visible infarction in five hearts removed 24 hours later. Additional data in this study suggest ^{67}Ga localization discriminates infarcted from normal or only transiently ischemic yocardium. ^{67}Ga scanning may prove particularly useful in the imaging of acute myocardial infarction in man.

868 Dimensional Changes of the Left Ventricle During Acute Pulmonary Arterial Hypertension in Dogs

EDWARD W. STOOL, CHARLES B. MULLINS, STEPHEN J. LESHIN and JERE H. MITCHELL

In these closed chest experiments in eight dogs progressive increases of 10 mm Hg in mean pulmonary arterial pressure increased right ventricular volume. Left ventricular volume began to decrease significantly at a mean pulmonary arterial pressure of 30 mm Hg, and was associated with a disproportionate reduction in left ventricular septal-lateral axis. During acute pulmonary hypertension progressive dilatation of the right ventricle caused a distinctive change in the left ventricular shape, suggesting septal bulging capable of impairing left ventricular function.

876 Ventricular Conduction Delay and Asystole During Systemic Hyperkalemia

PHILIP O. ETTINGER, TIMOTHY J. REGAN, HENRY A. OLDEWURTEL and MOHAMMAD I. KHAN

Systemic hyperkalemia induced in 30 intact dogs initiated A–V junctional delay and block followed by accelerated junctional pacemakers and ventricular conduction delays leading to unusual arrhythmias. Terminal Purkinje or Purkinje muscle block was the dominant mechanism of arrest with conduction through the ventricular specialized conduction system continuing at a regular rate even after asystole. In view of the absence of ischemia, conduction delays appear to be responsible for the abnormal ventricular function.

Continued on page A15

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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METHODS

887 Permanent Pervenous Transseptal Atrial Pacing. Canine Experiments and a Clinical Case

JOHN A. UDALL

Using a Ross needle to carry a 10 mm T-shaped electrode tip across the atrial septum, these investigators demonstrated the successful application and safety of permanent pervenous transseptal atrial pacing in a series of 10 dogs and finally in a 78 year old man suffering from carotid sinus syncope. The dog hearts were paced successfully for 3 to 12 months with average thresholds of 6 ma, and the patient became asymptomatic.

PEDIATRIC CARDIOLOGY

892 Evaluation of Patients with Pulmonary Atresia and Intact Ventricular Septum by Double Catheter Technique

ROBERT M. FREEDOM, ROBERT I. WHITE, Jr., CHARLES S. HO, ROBERT L. GINGELL, RICHARD E. HAWKER and RICHARD D. ROWE

This double catheter technique permitted simultaneous opacification of the pulmonary artery by way of the ductus arteriosus or systemic to pulmonary arterial anastomosis by one catheter and the right ventricle by the second catheter in five patients with pulmonary atresia. This technique is also applicable to patients with ventricular septal defect and acquired or congenital pulmonary atresia who have had palliative shunts, and to patients with complex transpositions and pulmonary atresia. Accurate definition of the type of pulmonary atresia by this technique should improve surgical results in these difficult cases.

896 Echocardiographic Assessment of Cardiac Malposition

RICHARD A. MEYER, DAVID C. SCHWARTZ, WESLEY COVITZ and SAMUEL KAPAN

Echocardiographic studies in 15 children with cardiac malposition demonstrate that this noninvasive technique and the knowledge of atrial situs determined from plain chest roentgenograms can define accurately important anatomic relations before cardiac catheterization and angiography.

HISTORICAL MILESTONES

904 Experimental Mitral Insufficiency (Bettelheim and Kauders)

SAUL JARCHO

Although performed at the end of the last century chiefly for clinical and physiologic purposes, these dog experiments on the production of mitral insufficiency clearly constitute a noteworthy historical introduction to this century's great advances in the surgical repair of heart valves in human beings.

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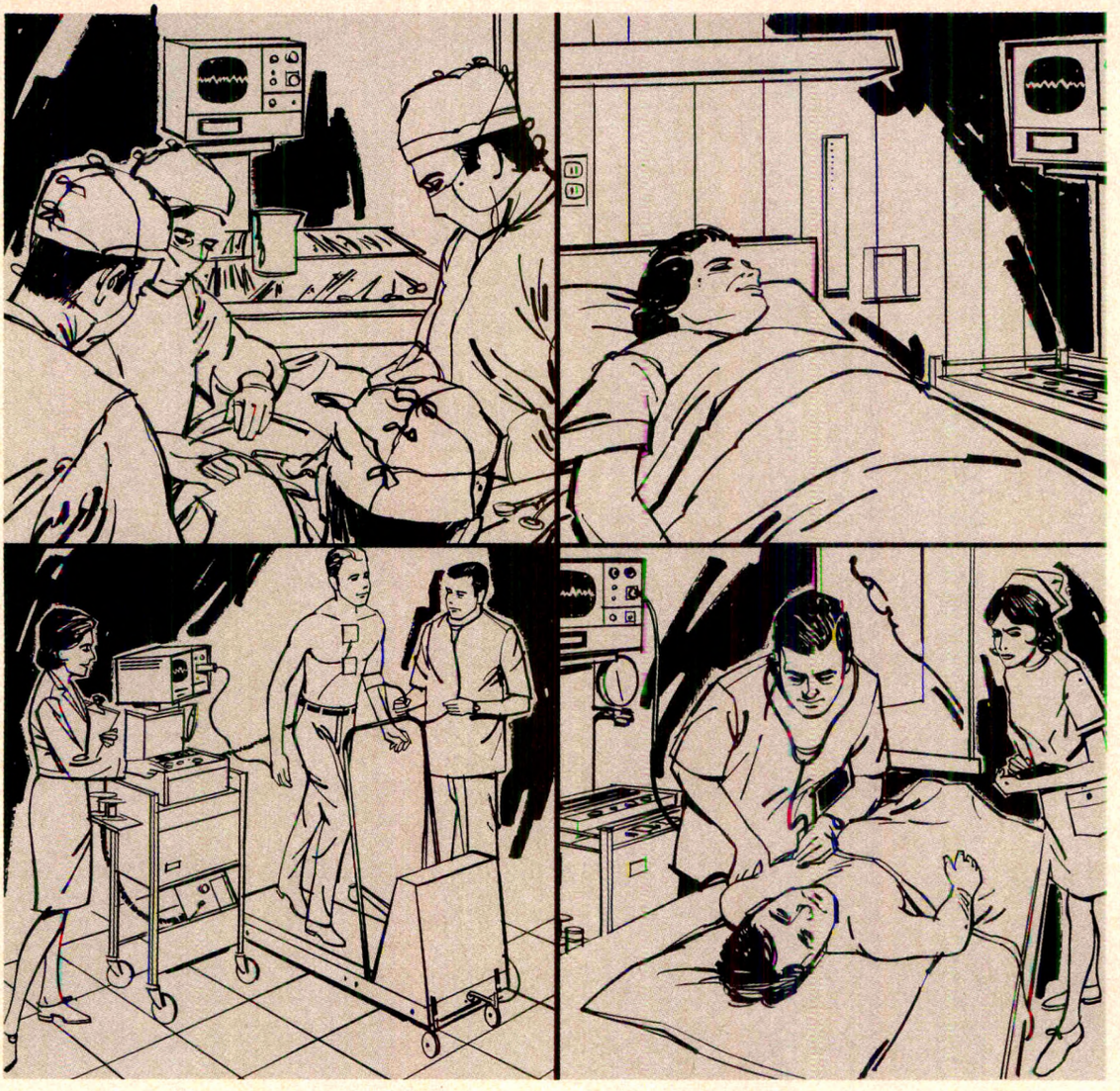

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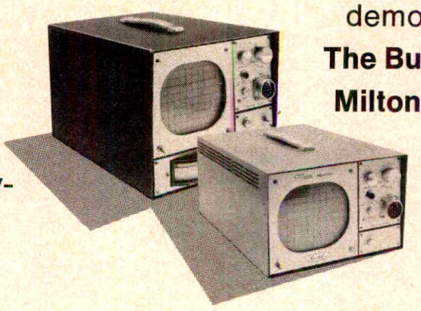

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908 Tachycardia-Dependent and Bradycardia-Dependent Mobitz Type II Atrioventricular Block Within the Bundle of His

MICHAEL A. GOODFRIEND and S. SERGE BAROLD

After excessive alcohol intake interesting rate-related transient second and third degree A–V block (Mobitz type II) with a normal QRS complex was noted in a 27 year old man. Electrograms demonstrated the lesion within the proximal portion of the His bundle.

914 Mitral and Tricuspid Lesions Associated with Polypoid Atrial Tumors, Including Myxoma

JOHN B. CARTER, RALPH CRAMER, Jr. and JESSE E. EDWARDS

Lesions of the mitral valve in seven of nine patients with left atrial tumors and of the tricuspid leaflets in two patients with right atrial myxoma are considered responses to the effects of friction by the tumor upon the surfaces involved.

920 Caseating Granulomas of the Heart

T. STERLING CLAIBORNE

Calcified masses within the myocardium of this 49 year old woman turned out on autopsy to be caseating granulomas, presumably due to tuberculosis, a most rare condition in this era of declining frequency of acid-fast infections.

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J. EDWARD OKIES and RICHARD P. ANDERSON

Two patients with symptomatic occlusion of a bypass graft during early convalescence were successfully treated by emergency operative thrombectomy and reanastomosis of the grafts. Coronary angiography to locate occluded grafts is indicated when signs and symptoms of myocardial ischemia reappear in the immediate postoperative period.

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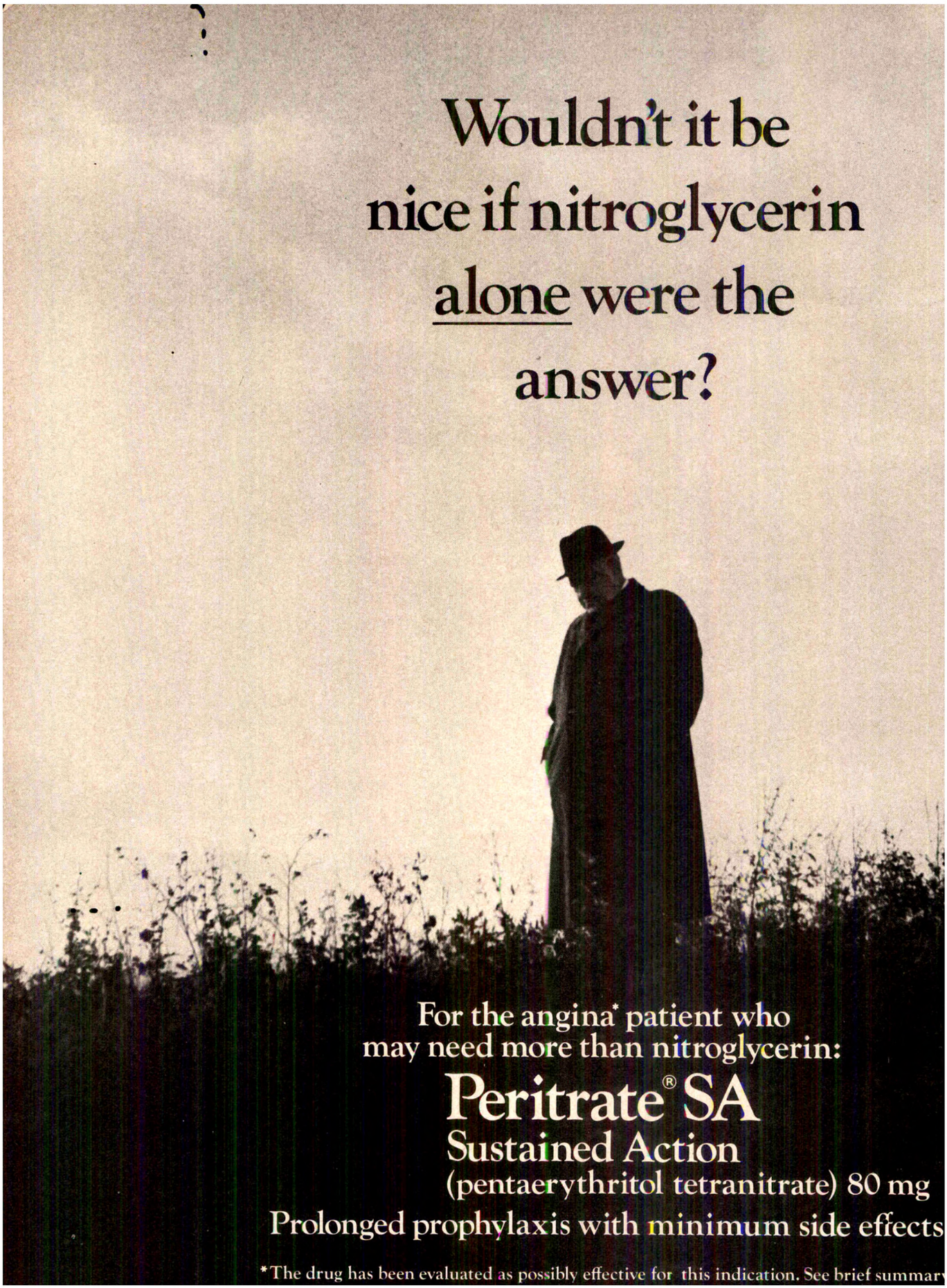
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Final classification of the less-than-effective indications requires further investigation.

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PE-GP-41

THE AMERICAN JOURNAL of CARDIOLOGY

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CORRECTION

The following changes, indicated in italics, should be made in the article by Dawson et al. in the April issue (Dawson JT, Hall RJ, Hallman GL, et al: Mortality in patients undergoing coronary artery bypass surgery after myocardial infarction. Am J Cardiol 33:483–486, 1974):

Page 483, last sentence: Electrocardiographic changes in *patients in Group 3* included development of Q waves in all but two patients.

Page 485, last line, column one: It is also apparent that early mortality in patients who undergo operation *31 to 60 days after* an acute myocardial infarction is no greater than in those who experience an infarction more than 2 months before operation.

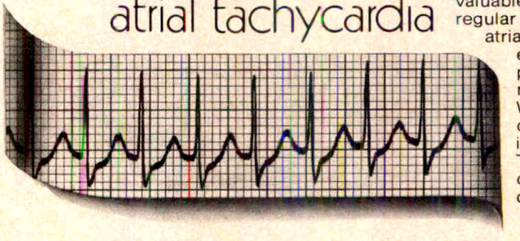
Page 496, line 3: The more severe complications, including shock and severe heart failure, were present only in patients operated on *less than 8 days* after infarction.

in the inner circle o
Inderal® stands ou

The place of INDERAL (propranolol hydrochloride) among the standard drugs for the treatment of disturbed cardiac rhythm has been frequently reaffirmed throughout seven years of clinical use. In fact, after withdrawal of digitalis, "...it may be the treatment of choice for digitalis-induced arrhythmias, provided hypokalemia is not present."[1] It has been widely used in selected supraventricular arrhythmias that have proved resistant to digitalis and in tachyarrhythmias precipitated by exercise, emotional stress, or undesirable sympathetic stimulation; and it is also effective in controlling supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome.[2]

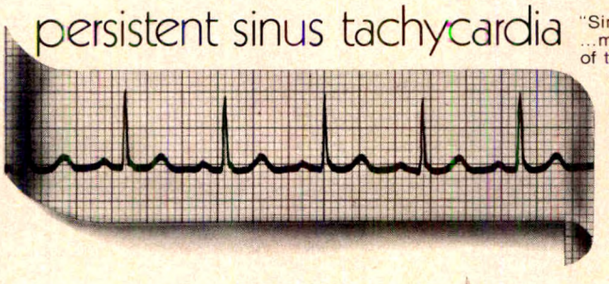
INDERAL protects the heart from undesirable catecholamine stimulation through its beta blocking action. Propranolol occupies the beta-receptor sites, making them unavailable to the beta-adrenergic stimulating effects of catecholamines. INDERAL is the first beta-adrenergic blocking agent in clinical cardiologic use.

paroxysmal atrial tachycardia



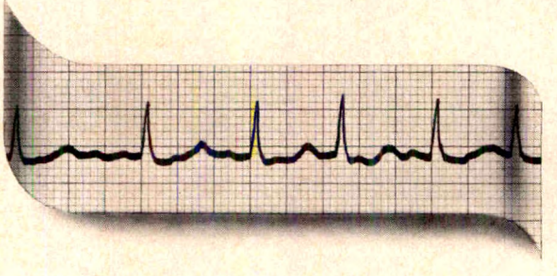
"In paroxysmal atrial tachycardia, the d slows the ventricular rate, and als valuable in restoring the heart regular sinus rhythm."[3] "Paroxys atrial tachycardia induced by ercise...has uniformly b prevented by propranolol," results with INDERAL in Wolff-Parkinson-White s drome"...have been favor in all but a few patients repo This condition appears to one of the more definite i cations for propranolol."[4]

persistent sinus tachycardia



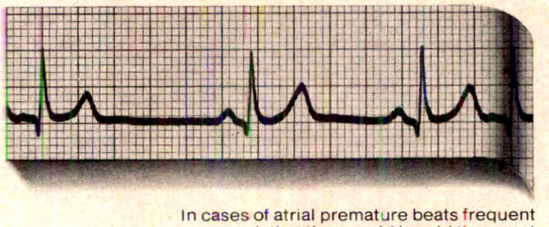
"Sinus tachycardia induced by stress ...may be inappropriate to the needs of the patient and, in fact, may be causing symptoms of itself. If the clinical situation does not suggest a needed compensatory sinus tachycardia and the heart rate is indeed inappropriate, treatment with propranolol has been successful."[4]

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism, it has proved useful for this purpose. "Sinus tachycardia in hyperthyroidism which causes symptoms may be relieved by the administration of propranolol before definitive therapy....The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated using modest doses of propranolol."[4]

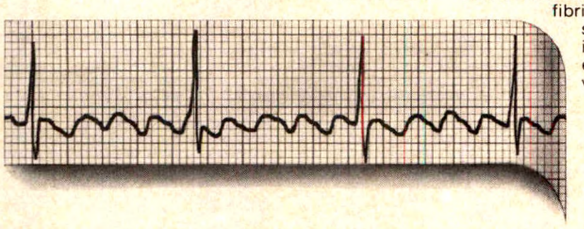
persistent atrial extrasystoles



In cases of atrial premature beats frequent enough that they could herald the onset of atrial fibrillation, it has been recommended that propranolol be used after other measures have failed to control the beats.[5]

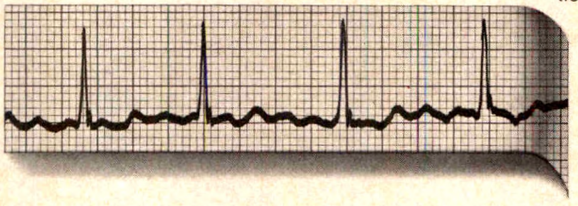
antiarrhythmia agents for supraventricular arrhythmias

atrial flutter



"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not controlled by digitalis, especially in the presence of mitral valve disease."[6]

atrial fibrillation

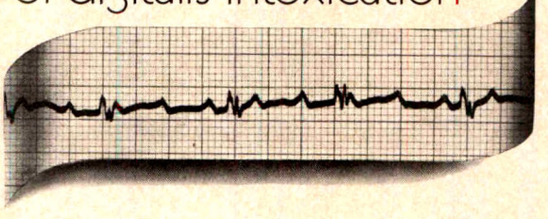


"One salutary effect of propranolol is slowing of the ventricular rate in atrial flutter and fibrillation."[4] In a review of the literature, it was noted that most patients with fibrillation not controlled by digitalis alone experienced slowing of the ventricular rate after administration of propranolol and a few reverted to sinus rhythm.[7]

---

and for tachyarrhythmias of digitalis intoxication

"Propranolol is very effective in treating arrhythmias caused by digitalis excess. Its use in this setting may be limited by the presence of significant congestive heart failure or heart block, both of which can be potentiated by propranolol. However, if given in small doses with careful monitoring, it is often of great value in the treatment of digitalis toxicity."[5]



References 1. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 2. Chung, E.K.: Postgrad. Med. *53*:107 (Apr.) 1973. 3. Harrison, D.C.: Clinical Guide to the Use of Beta-Adrenergic Blockade in Arrhythmias, Ayerst Laboratories, 1971, p. 10. 4. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 5. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 6. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971, p. 7. 7. Gibson, D., and Sowton, E.: Prog. Cardiovasc. Dis. *12*:16 (July) 1969.

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helps prevent or control catecholamine-induced cardiac arrhythmias

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(See last page of advertisement for prescribing information.)

BRIEF SUMMARY
(For full prescribing information, see package circular.)

Inderal®

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A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS:

Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias
With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia.
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis
INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma
After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED: BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride) TABLETS No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

7420

On Reliability and a Pound of Flesh

The life's blood of an electrocardiograph is the chart that flows through it.

Assurance that the recording is totally reliable depends, in part, on the quality of the chart itself.

Charts, as provided by the instrument maker, afford this assurance to a maxima ... because they are designed as an integral part of the instrument.

Charts, as provided by others, are imitations at best. They may save a few pennies, but not without risk of shedding a "drop of reliability".

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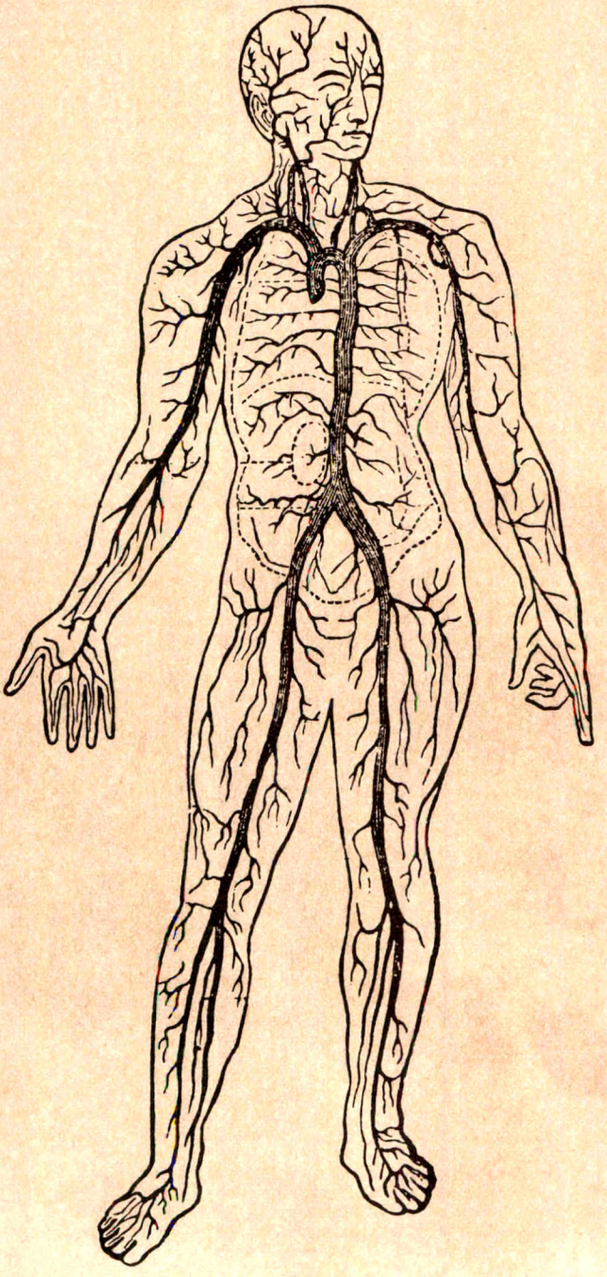
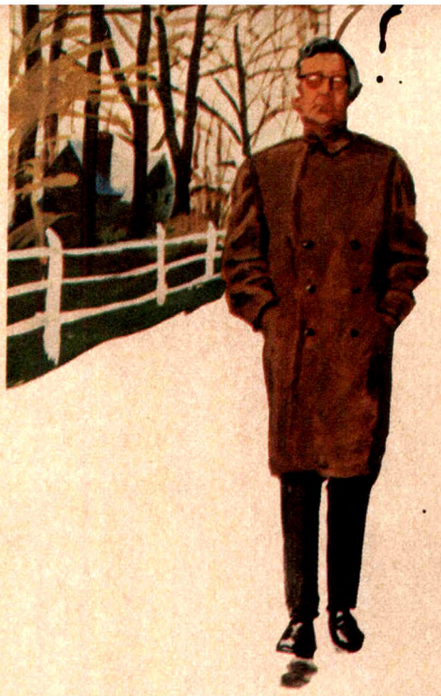


If psychic tension interferes with cardiac rehabilitation, here's how Valium® can help.
(diazepam)

During hospitalization, Valium (diazepam) can relieve psychic tension that can disrup bed rest and interfere with the rehabilitation program.

After the MI patient is stabilized, a certain amount of psychic tension is to be expected. Your reassurance, counseling and enlistment of family support can often minimize its effects. However, in some instances, the patient's thoughts may dwell constantly on his condition and how it will affect his life, thus producing excessive psychic tension that ma present special problems. He may feel overwhelmed and be so burdened by these tensions that he is unable to rest and unable or unwilling to begin a program of rehabilitatior Under these circumstances, Valium® (diazepam) can often be a beneficial adjunct.

Valium can calm the cardiac patient and help reduce his psychic tension to appropri ate levels. Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticoagulants, anticholinergics and antacids. Careful consideration should be given to the pharmacology of agents used with Valium, particularly those which may potentiate its action.



During convalescence at home, Valium (diazepam) can reduce excessive anxiety that may hinder participation in active rehabilitation.

Your counseling and the family's support do much to control the anxieties that may interfere with this stage of convalescence—a time when you may wish to encourage a gradual increase in activity. But in some patients, excessive anxiety may retard general progress. For them, Valium can be beneficial during the post-hospital transition to full ambulation. And, because the convalescent cardiac patient may be particularly prone to excessive tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *b.i.d.* or *t.i.d.* schedule can reduce these symptoms and thus may encourage sleep. Therapy with Valium should be discontinued when symptoms have been reduced to tolerable levels.

What an informed cardiac patient should know about Valium therapy.

The cardiac patient should know that he can generally expect Valium to help relax and calm him so that he won't feel so overwhelmed by his tension and anxiety. An explanation of the importance of the dosage regimen you prescribe may go a long way to ensure his cooperation. As with all CNS-acting agents, the patient taking Valium should be cautioned against driving or operating dangerous machinery.

Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets can relieve the cardiac patient's undue psychic tension

ROCHE

For a summary of product information, see the following page.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets
can relieve the cardiac patient's undue psychic tension

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 100.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Now, when you turn on increased cardiac output, vital organ perfusion and renal flow . . .

. . . you don't have to turn on the high risk of undesirable effects.

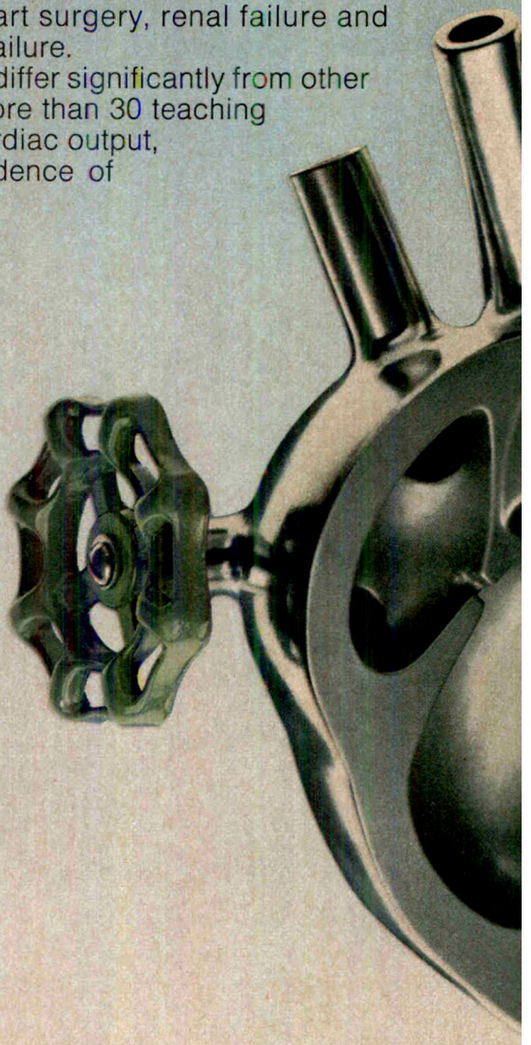
Introducing INTROPIN® (dopamine HCl)
for the correction of hemodynamic imbalances in the shock syndrome
due to: myocardial infarction, trauma, endotoxic septicemia,
open heart surgery, renal failure
and cardiac decompensation as in congestive failure.

Complete product information and a Clinical Reprint Order Form appear on the last two pages of this advertisement.

INTROPIN® (dopamine HCl) can increa
without the high r

Intropin is indicated for the correction of hemodynamic imbalances in the shock syndrome due to: myocardial infarction, open heart surgery, renal failure and chronic cardiac decompensation as in congestive failure.

The pharmacological actions of Intropin appear to differ significantly from other catecholamines. Over 6 years of clinical trials at more than 30 teaching hospitals have shown that Intropin can increase cardiac output, vital organ perfusion and renal flow with a low incidence of undesirable effects.



INTROPIN usually will:

increase perfusion to vital organs

Multiclinic trials have demonstrated that Intropin provides adequate perfusion of vital organs. This is based upon a number of clinical parameters including an increase in urine flow which appears to be one of the better diagnostic signs of increased vital organ perfusion.

At doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage.

increase urine output

Intropin significantly increases urine flow. This is in contrast to most other sympathomimetic amines, which usually cause little or no significant increase in urine output.

This increased urine output is due to increases in glomerular filtration rate and renal blood flow and is accompanied by increased sodium excretion. Intropin may also increase urine flow in patients whose urine output is within normal limits and may promote diuresis usually with no decrease in osmolality.

increase cardiac output

Intropin acts predominantly on the beta receptors of the heart to substantially increase contractility, stroke volume and cardiac output, as confirmed by invasive technique.

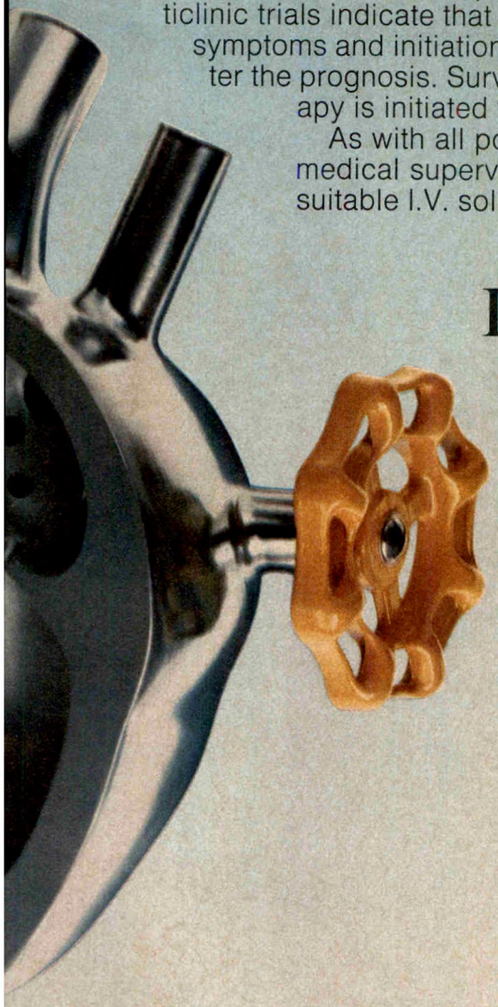
increase blood pressure

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of Intropin. Prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer Intropin as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

rdiac output and vital organ perfusion undesirable effects.

Patients most likely to respond adequately to Intropin are those in whom urine flow, myocardial function and blood pressure have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and Intropin, the better the prognosis. Survival rates are considerably improved when Intropin therapy is initiated within 4 hours of onset of symptoms.

As with all potent drugs, Intropin must be administered under close medical supervision. It is administered only by I.V. drip after dilution in a suitable I.V. solution.



INTROPIN usually will not:

cause excessive myocardial oxygen consumption

Intropin produces less increase in myocardial oxygen consumption than isoproterenol. During administration of Intropin, the myocardial oxygen supply/demand ratio has usually remained stable. Intropin appears to meet additional myocardial oxygen requirements by increasing coronary flow.

substantially increase tachyarrhythmias

One investigator reported less than a 3% incidence of tachyarrhythmias in clinical trials in 270 patients. The tachyarrhythmias which occurred were easily managed.

increase total peripheral resistance

Administration of Intropin, at low and intermediate dosages, generally does not increase total peripheral vascular resistance. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases.

Serious undesirable effects seldom occur.

In multiclinic studies, adverse reactions necessitated discontinuation of Intropin therapy in only 11 (2%) of 526 patients.

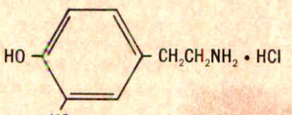
Additional product information and a Clinical Reprint Order Form appear on the following pages.

ARNAR-STONE LABORATORIES, INC.

INTROPIN® (dopamine HCl)

5 ml. AMPUL / FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3,4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximating 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential for risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

If a disproportionate rise in the diastolic pressure (i.e., a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Although in clinical trials inadvertent subcutaneous infiltration did not produce any evidence of necrosis, the usual precautions should be taken to avoid extravasation.

Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: THIS IS A POTENT DRUG. IT MUST BE DILUTED BEFORE ADMINISTRATION TO PATIENT.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:

250 ml. dilution contains 800 mcg./ml. of INTROPIN

500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg/kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

ARNAR-STONE LABORATORIES, INC.
A Subsidiary of American Hospital Supply Corporation
Mount Prospect, Illinois 60056

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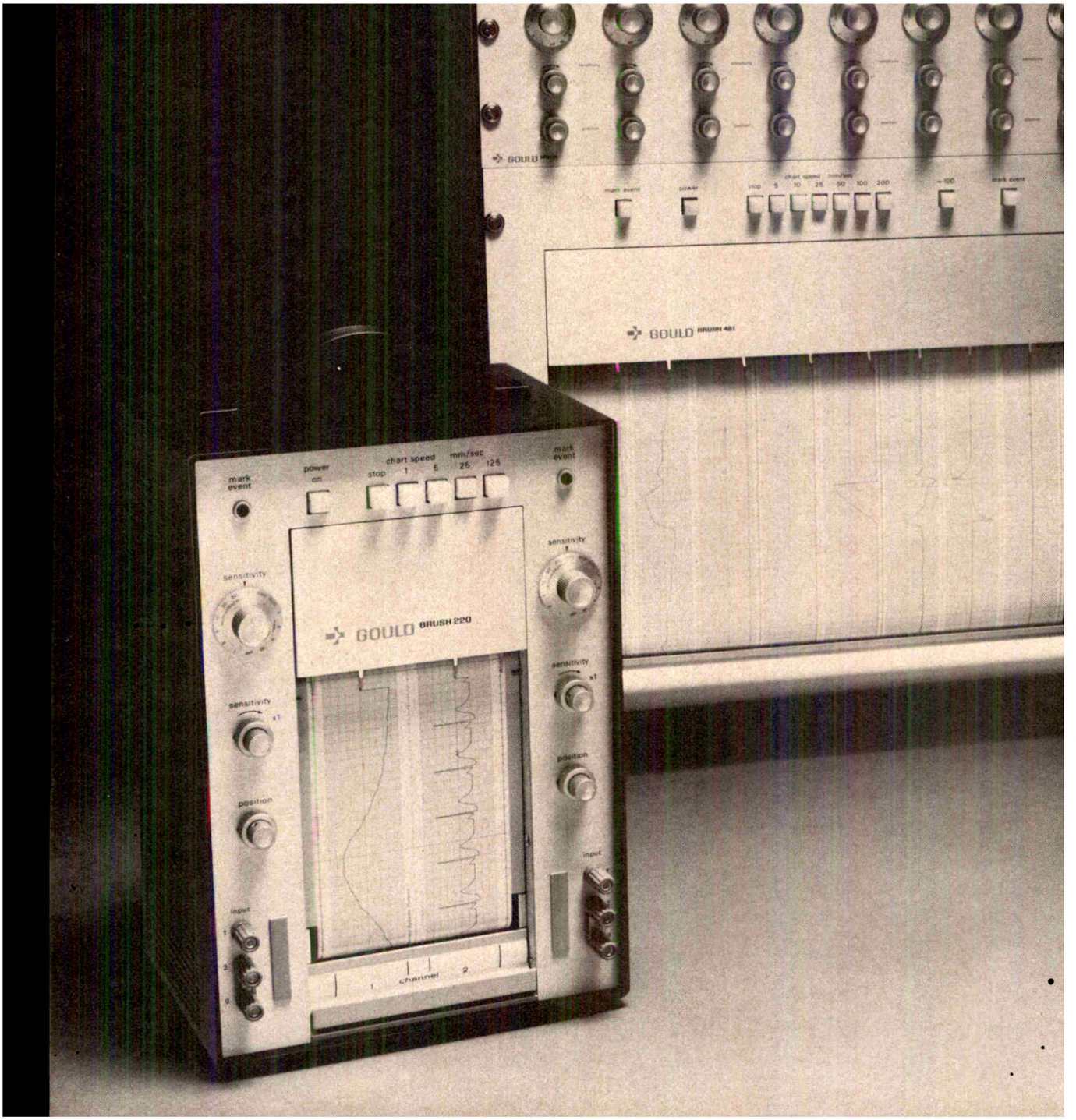
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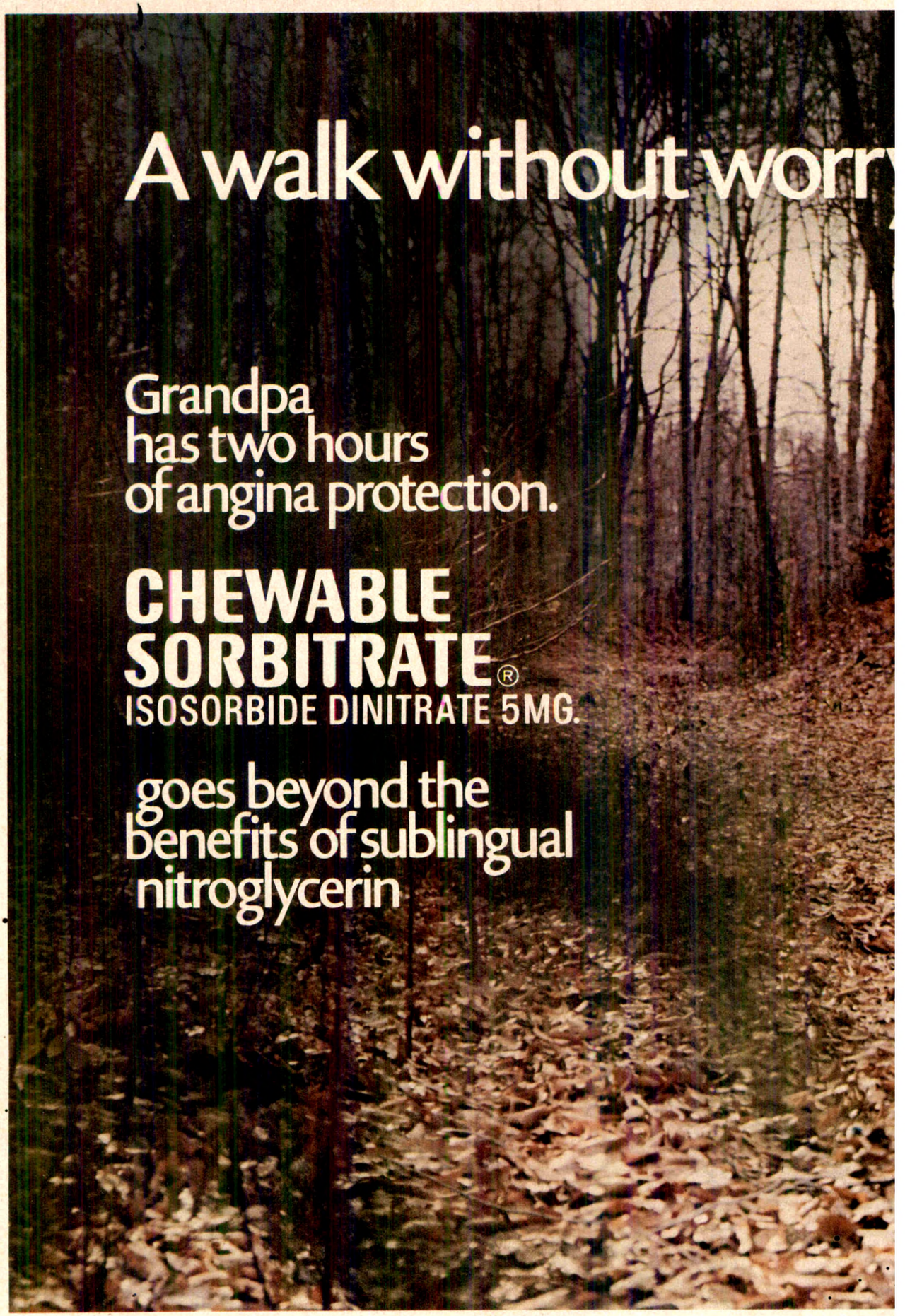
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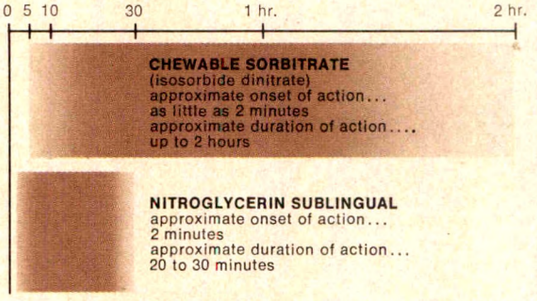

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☐ And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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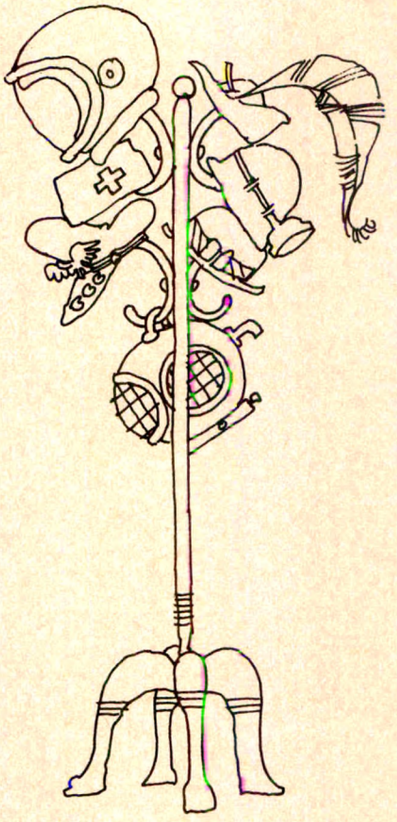
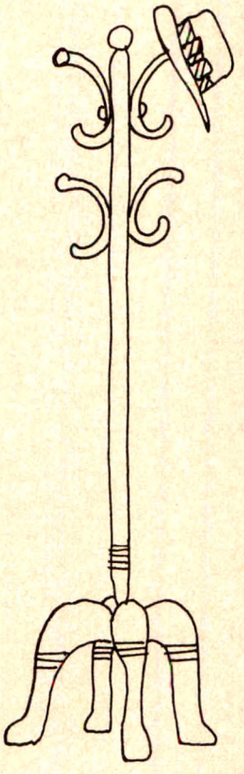


The cure:



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The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

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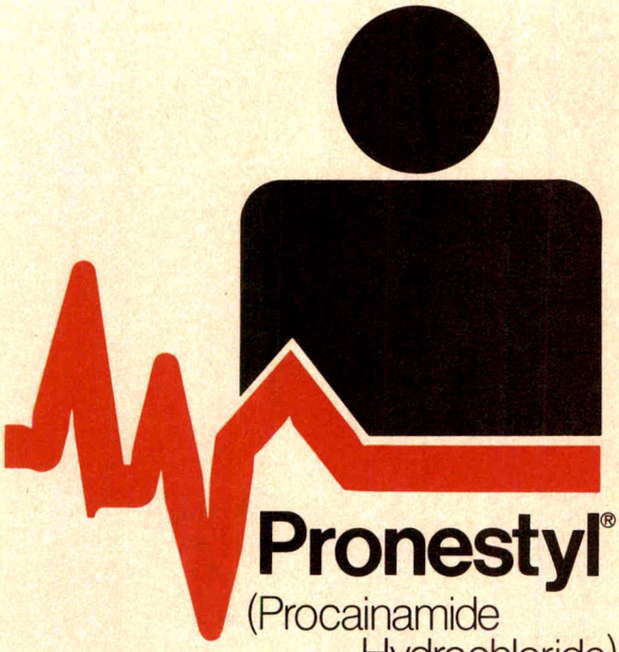
At the first sign of trouble



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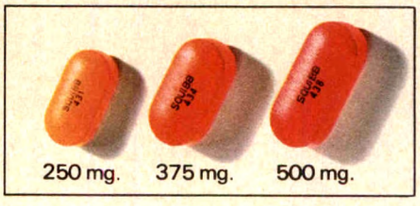

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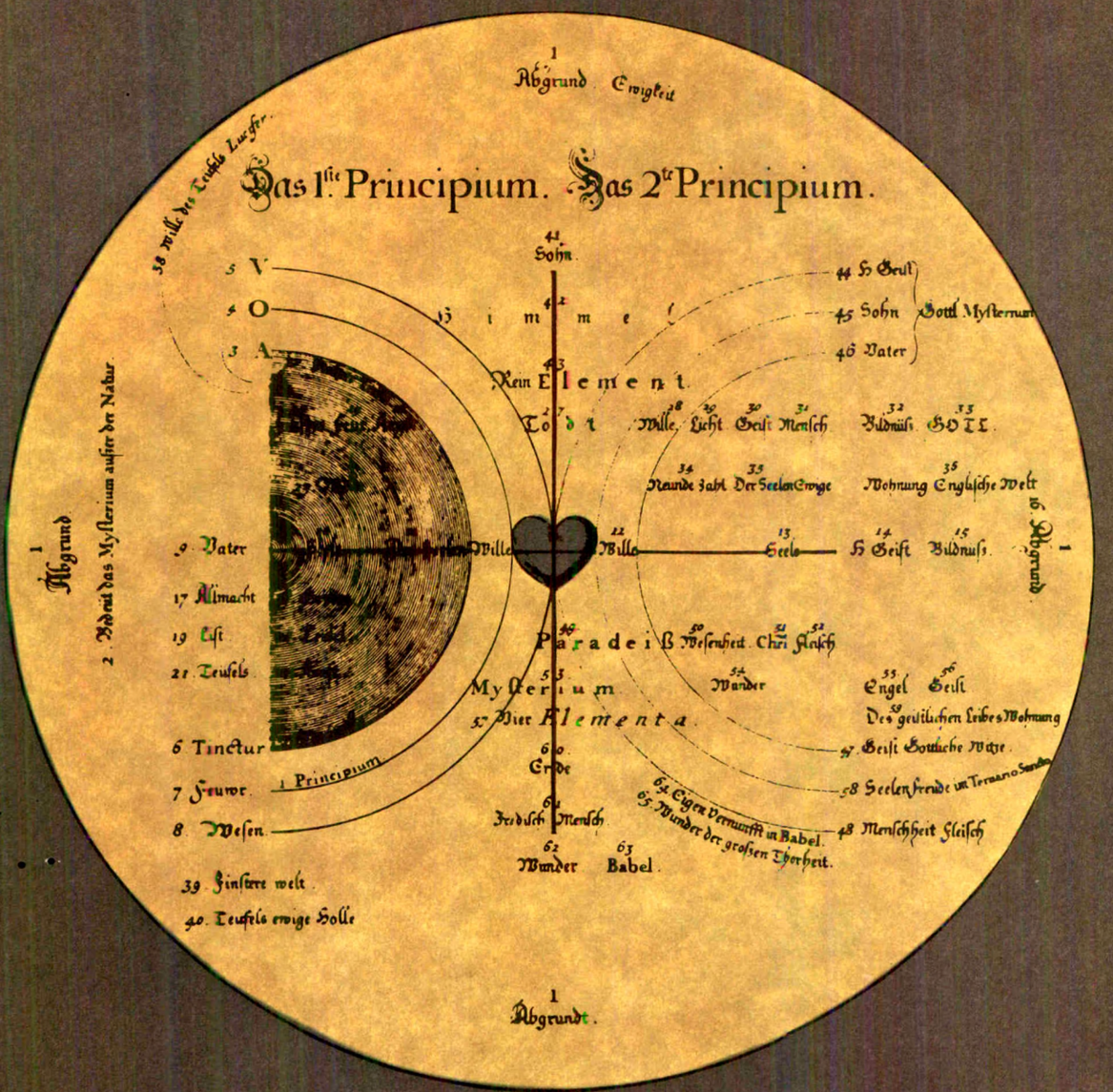

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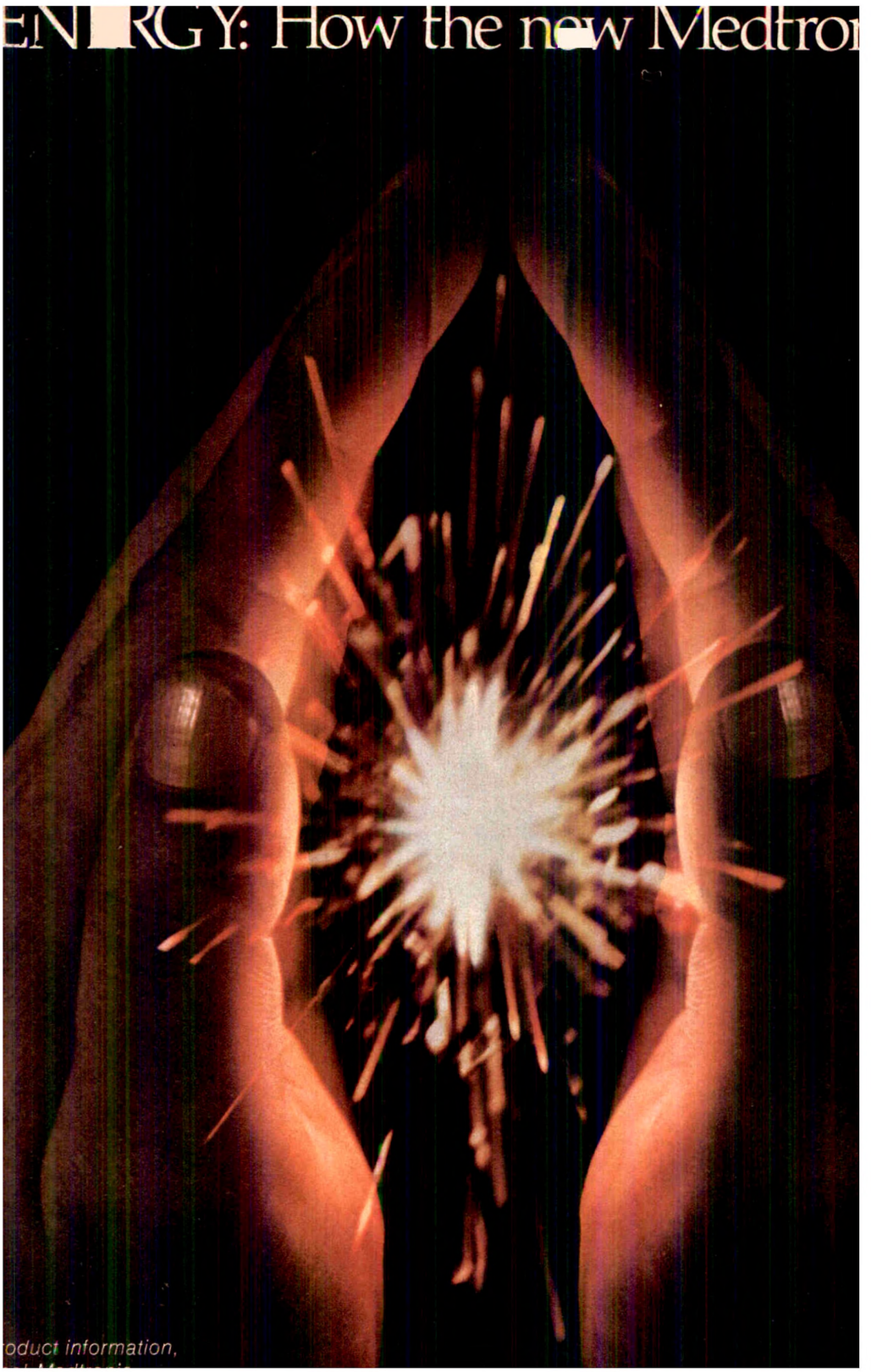
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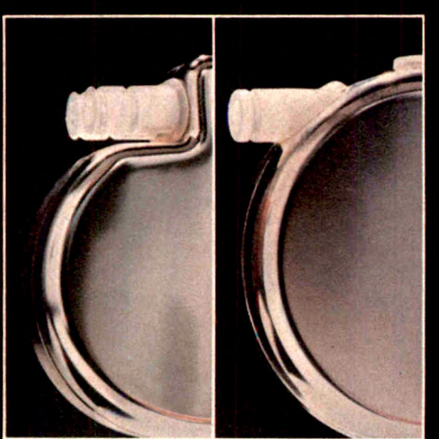

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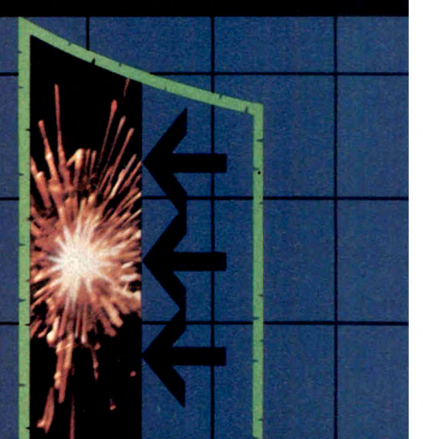

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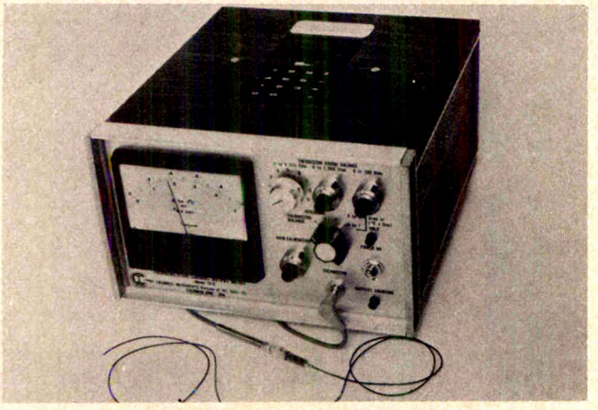

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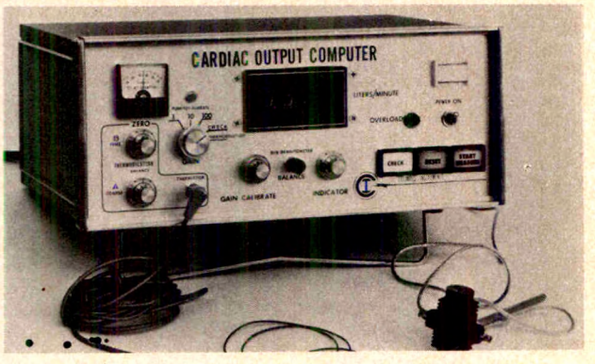

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

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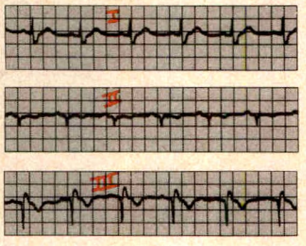
The Somatic Protest in the Postcoronary Patient...

Physiologic reaction to excessive anxiety



Although he has valid reason for concern, the person convalescing from myocardial infarction may react to his illness with *disproportionate* anxiety, which can hinder smooth recovery and rehabilitation. Undue anxiety and emotional tension may, in some patients—because of marked increase in catecholamine excretion during stay in, and on day of transfer from, the CCU—cause increased heart rate, increased cardiac output and intensified oxygen consumption by heart muscle. In addition, excessive anxiety can (1) increase feelings of frustration at forced inactivity, (2) foster undue preoccupation with heart function, (3) diminish capacity to tolerate prospect of work stress and (4) retard rehabilitation. A calm outlook and reduction of excessive emotional stress are thus desirable.

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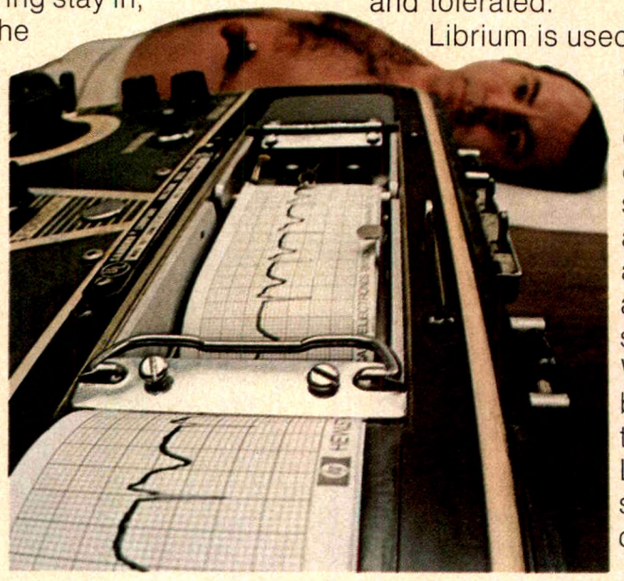

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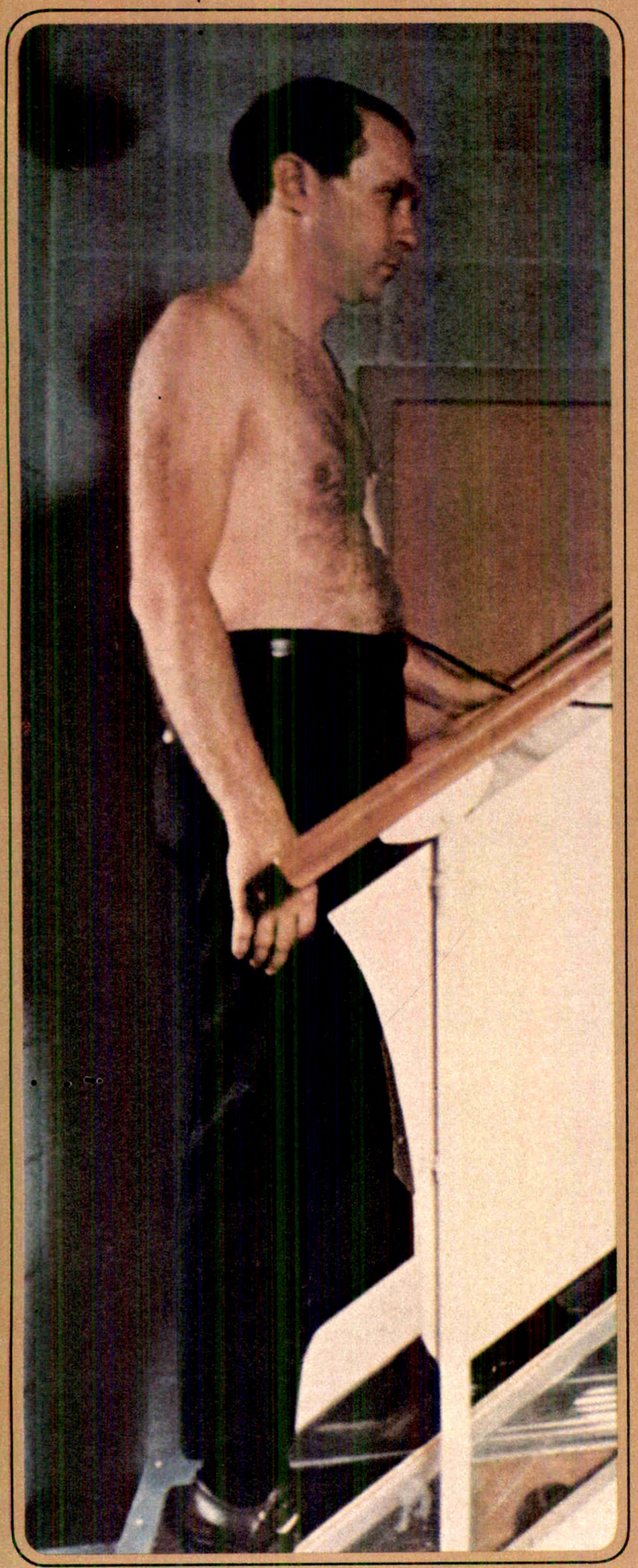

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The American Journal of CARDIOLOGY®

VOLUME 33

NUMBER 7

CLINICAL STUDIES

Hemodynamic Effects of Noninvasive Systolic Unloading (Nitroprusside) and Diastolic Augmentation (External Counterpulsation) in Patients with Acute Myocardial Infarction

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The two major beneficial hemodynamic effects of invasive circulatory assistance (intraaortic balloon pumping) are (1) left ventricular systolic unloading, and (2) diastolic augmentation of aortic pressure. In this study, these effects were produced noninvasively in 17 patients (13 with acute myocardial infarction, 5 of whom had cardiogenic shock). Systolic unloading produced by the constant intravenous infusion of sodium nitroprusside (16 to 200 μg/min) caused a reduction in pulmonary capillary wedge pressure (27 to 19 mm Hg), a rise in cardiac index (1.71 to 2.25 liters/min per m^2), and a reduction in mean arterial pressure (81 to 73 mm Hg). Diastolic augmentation with external counterpulsation produced a 20 mm Hg increase in peak, and a 7 mm Hg increase in mean diastolic arterial pressure. Cardiac index rose 14 percent after external counterpulsation in the patients with acute myocardial infarction. The results of combined use of these two modes of therapy (nitroprusside plus external counterpulsation) were better than those of either alone, in that external counterpulsation reversed the decrease in diastolic arterial pressure produced by nitroprusside, and also increased cardiac index further in six of nine patients. Thus it is feasible to utilize the principles of invasive circulatory assistance in a noninvasive way to produce hemodynamic improvement in patients with acute myocardial infarction.

The two major beneficial hemodynamic effects of invasive circulatory assistance appear to be (1) left ventricular systolic unloading, and (2) diastolic augmentation of aortic pressure. Systolic unloading permits an increased stroke volume at the same end-diastolic fiber length and also reduces myocardial oxygen demand by reducing the tension-time index. Subsequent reduction in heart size due to more complete systolic emptying will further reduce myocardial oxygen demand. By contrast, diastolic augmentation increases coronary perfusion pressure and thus helps to maintain coronary flow, particularly in the presence of partial obstruction of the coronary arteries.

Devices such as the intraaortic balloon which produce these two effects have been shown to have beneficial effects in some patients with

This study was supported in part by Contract NIH-PH-43-68-1333 under Myocardial Infarction Program, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. Manuscript accepted November 28, 1973.

* This work was performed during the tenure of an established investigatorship of the American Heart Association.

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TABLE I

Characteristics of Patient Population

Group	Age (yr) Mean	Age (yr) Range	Sex	Clinical Class (Killip)	Deaths (no.)
No MI* (4)	63	52–74	M (4)	I (1)	
				III (2)	
				IV (1)	1
MI only (8)	57	35–73	M (6)	I (2)	
			F (2)	II (2)	
				III (4)	2
MI + shock (5)	64	51–71	M (5)	IV (5)	3

* Two with coronary artery disease, and two with cardiomyopathy.

Figures in parentheses indicate number of patients; MI = myocardial infarction.

acute myocardial infarction and pump failure.[1] However, the use of these invasive devices for circulatory assistance requires a specially trained surgical-medical team and has generally been restricted to selected research centers. If similar hemodynamic effects could be obtained in a noninvasive manner, such benefit would be more widely applicable to patients with pump failure after acute myocardial infarction.

Several recent studies have shown that systolic unloading with vasodilator drugs such as nitroprusside or phentolamine can improve hemodynamic performance in pump failure complicating acute myocardial infarction.[2–5] However, such agents also reduce arterial diastolic pressure because of their nonselective action relative to the cardiac cycle. This reduction in the coronary arterial perfusing pressure might further compromise coronary blood flow and produce hemodynamic deterioration. On the other hand, noninvasive external counterpulsation has been found to be effective in increasing diastolic perfusing pressure.[6] A combination of these two therapeutic maneuvers might complement each other and thus provide a simple, noninvasive application of the principles of invasive circulatory assistance. Accordingly, this study was designed to determine the separate and combined effects of these two therapeutic modalities on hemodynamics and cardiac metabolism in patients with acute myocardial infarction.

Methods

Patient population and measurements: Seventeen patients underwent external counterpulsation (Cardiassist®, Medical Innovations, Inc., Waltham, Mass.) for at least 1 hour. Thirteen of these patients had acute myocardial infarction, and 5 of the 13 had clinical cardiogenic shock. The four patients without infarction included two with coronary artery disease and two with cardiomyopathy (Table I). Control hemodynamic measurements were obtained after admission of the patients to the Myocardial Infarction Research Unit. Arterial pressure (AP) was monitored through a 20 gauge cannula inserted into the radial artery. Right atrial (RA), pulmonary arterial (PA) and pulmonary capillary wedge (PCW) pressures were recorded through a balloon-tipped catheter.[7] At least five pressure cycles were measured and averaged for each single reading. Cardiac output (CO) was measured by the thermodilution technique in triplicate with the same catheter. Individual variation in triplicate measurements is generally 5 to 10 percent. In seven patients, coronary sinus flow was measured by a constant infusion thermodilution technique.[8] Minute to minute variation in this measurement is 5 to 10 percent if hemodynamic status remains stable. For this determination a special preshaped catheter was inserted into the coronary sinus. Blood samples from the coronary sinus and radial artery were analyzed for pH, PCO_2, and PO_2 by a pH gas analyzer (model 113, Instrumentation Laboratories). Hemoglobin saturation was determined with a co-oximeter (model 182, Instrumentation Laboratories, Lexington, Mass). The mean difference between paired samples was less than 1 percent. Samples of arterial and coronary sinus blood were also obtained for determination of lactate concentration by an automated modification of the enzymatic method of Hohorst.[9]

Derived hemodynamic and metabolic measurements were calculated as follows: Stroke work index (SWI) = stroke volume index (SVI) × ($\overline{AP}$ − $\overline{PCW}$) × 0.144 (g-m/m^2); systemic vascular resistance (SVR) = 80 ($\overline{AP}$ − $\overline{RA}$)/CO (dynes sec cm^{-5}); oxygen content (ml/100 ml) = hemoglobin saturation × hemoglobin content (g/100 ml) × 1.34;

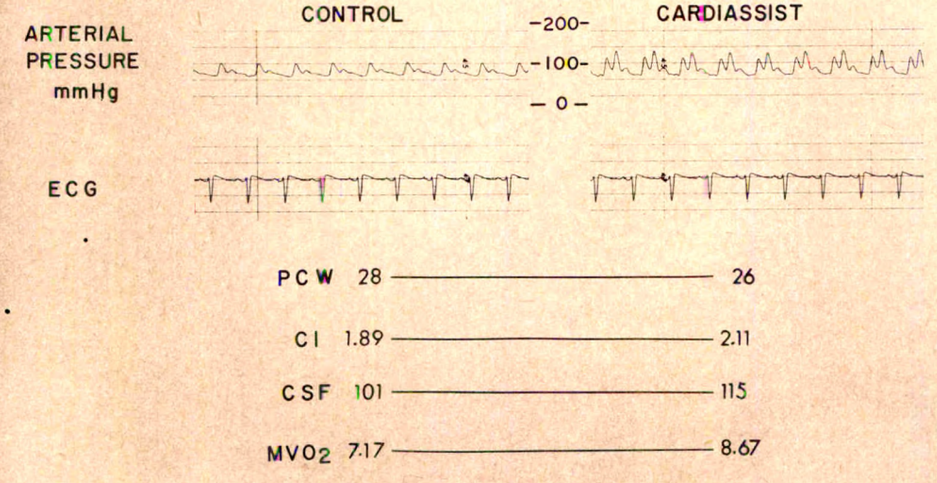

FIGURE 1. Tracings before and during external counterpulsation in a representative patient with acute myocardial infarction and moderate pump failure. Diastolic augmentation of pressure is seen in the arterial pressure tracing at right. CI = cardiac index (liters/min per m^2); CSF = coronary sinus flow (ml/min); ECG = electrocardiogram; MVO_2 = myocardial oxygen consumption (ml/min); PCW = pulmonary capillary wedge pressure (mm Hg).

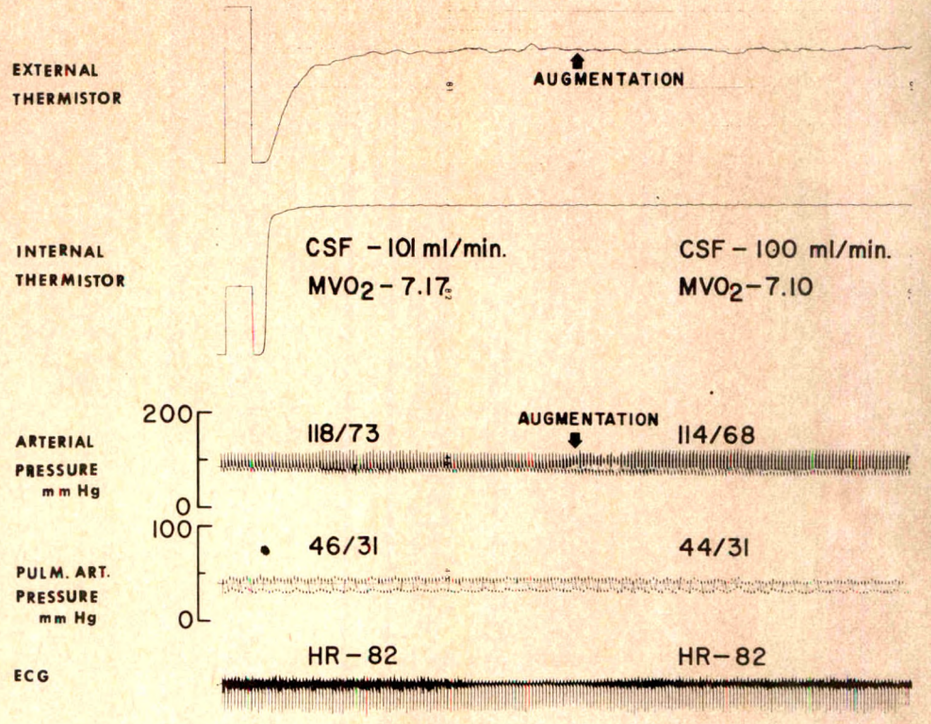

FIGURE 2. Tracings obtained during the measurement of coronary sinus flow in a representative patient with acute myocardial infarction. The upper two tracings represent temperature recordings from the external and internal thermistors of the coronary sinus catheter. After initial calibration there was a continuous infusion of cold 5 percent dextrose in water until a constant temperature and flow rate (101 ml/min) were achieved. Diastolic augmentation was initiated at the **arrow.** HR = heart rate (beats/min); PULM. ART. = pulmonary arterial; other abbreviations as in Figure 1.

myocardial oxygen consumption (ml/min) = [arterial-coronary sinus oxygen content (ml/100 ml)] × [coronary sinus blood flow (ml/min) × 10^{-2}]; myocardial lactate extraction (percent) = (arterial-coronary sinus lactate)/arterial lactate.

Systolic unloading with nitroprusside: Nitroprusside was administered intravenously at a rate of 16 to 200 μg/min with the use of an infusion flow controller (Ivac 200, Ivac Corporation, San Diego, Calif.). The infusion rate of nitroprusside was gradually increased until the mean arterial pressure decreased by not more than 20 mm Hg or until there was a significant decrease (more than 5 mm Hg) in the pulmonary capillary wedge pressure. The infusion rate of nitroprusside was then kept constant, and hemodynamic and metabolic measurements were repeated. Patients were given maintenance doses of nitroprusside for a minimum of several hours, and in many instances for periods ranging up to several days.

Diastolic augmentation with external counterpulsation: The Cardiassist device was placed over the lower legs of the patient and adjusted comfortably. External counterpulsation synchronized with the electrocardiogram was applied in diastole to produce satisfactory visual augmentation of the arterial diastolic pressure on the oscilloscope. External counterpulsation pressures ranged from 150 to 250 mm Hg depending on patient comfort and the hemodynamic results.

After initial hemodynamic measurements, external counterpulsation was applied for at least 1 hour. Hemodynamic measurements were then repeated while the assist device was in use. In the nine patients who subsequently received nitroprusside, the external counterpulsation was discontinued and the hemodynamic measurements were repeated. During nitroprusside administration hemodynamic measurements were obtained and then external counterpulsation was added for periods of 1 hour to evaluate the additive effects of the two modalities on hemodynamics. In general, nitroprusside therapy was used as the primary therapeutic intervention, whereas external counterpulsation was added periodically.

Results

Results of External Counterpulsation

Figure 1 illustrates the representative hemodynamic effects of external counterpulsation in a patient with myocardial infarction and moderate pump failure. The augmentation of diastolic pressure is illustrated in the right panel of the arterial pressure tracing. During external counterpulsation, this patient had a slight increase in systolic pressure, with no change in heart rate or pulmonary capillary wedge pressure. There was a 10 percent increase in cardiac index. The slight increase in coronary sinus flow and myocardial oxygen consumption ($M\dot{V}O_2$) was probably secondary to the increase in systolic pressure and time-tension index.

When there was little change in the systolic pressure, external counterpulsation and diastolic augmentation did not, in general, appear to affect the level of coronary sinus flow, as shown by tracings from a representative patient in Figure 2. External counterpulsation with diastolic augmentation, was begun at the arrow. The temperature record of the external thermistor **(top panel)** was not altered by diastolic augmentation although mean diastolic pressure was increased by 7 mm Hg. Thus, coronary sinus flow and $M\dot{V}O_2$ were unchanged.

Figure 3 shows the effects of external counterpulsation on peak and mean diastolic pressures in all patients studied. There was a statistically significant

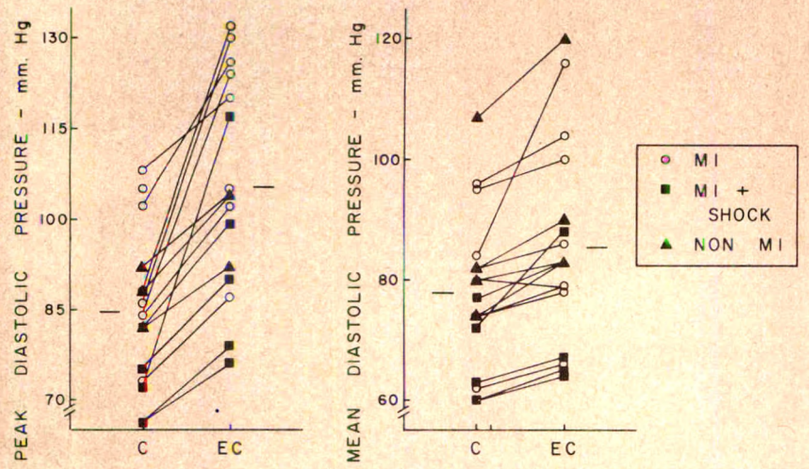

FIGURE 3. Effects of external counterpulsation (EC) on arterial diastolic pressure in three subgroups of patients. Individual patients before (C) and during external counterpulsation are indicated by the appropriate symbols connected by a line. The lines to the side of the data indicate the means for the entire group. MI = myocardial infarction.

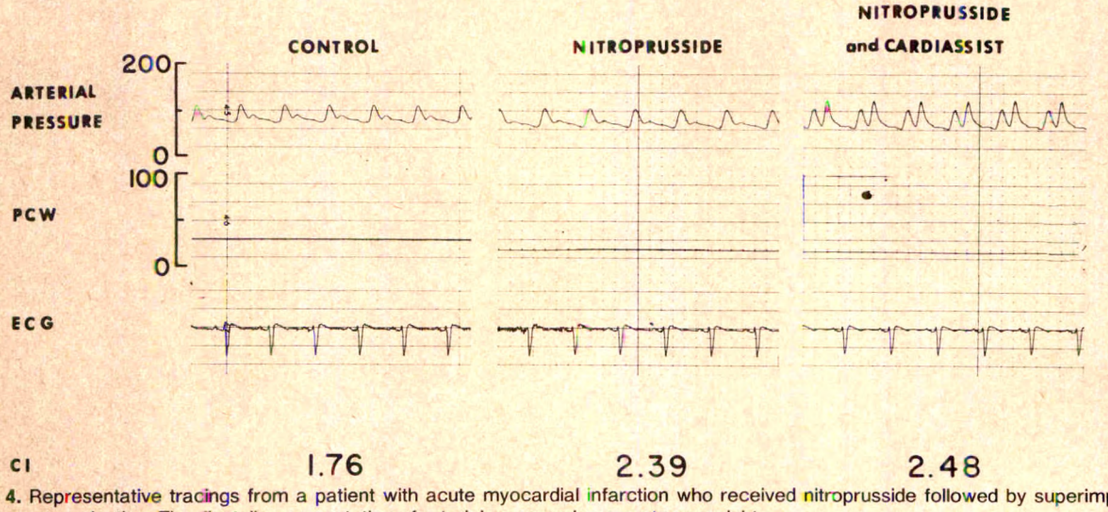

FIGURE 4. Representative tracings from a patient with acute myocardial infarction who received nitroprusside followed by superimposition of external counterpulsation. The diastolic augmentation of arterial pressure is seen at upper right.

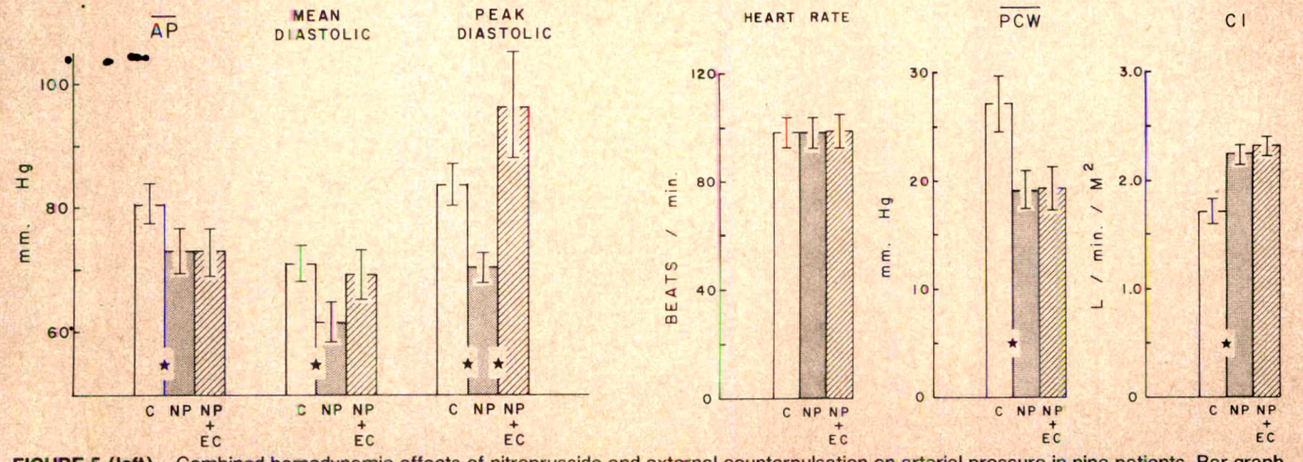

FIGURE 5 (left). Combined hemodynamic effects of nitroprusside and external counterpulsation on arterial pressure in nine patients. Bar graph results are presented as means ± standard error of the means. The **star** between adjacent bars indicates statistical differences by paired *t* testing ($P < 0.05$). $\overline{AP}$ = mean pressure; C = control; NP = nitroprusside; NP + EC = nitroprusside + external counterpulsation.

FIGURE 6 (right). Combined hemodynamic effects of nitroprusside and external counterpulsation on heart rate, mean capillary wedge pressure ($\overline{PCW}$) and cardiac index in nine patients with acute myocardial infarction. Format as in Figure 5.

increase in peak (average 20 mm Hg) and in mean (7 mm Hg) diastolic pressure. The combined hemodynamic effects of external counterpulsation in all patients are summarized in Table II. In both groups of patients with myocardial infarction, there was also a statistically significant increase in cardiac index (average 14 percent) and in stroke work index (average 25 percent). There were no significant changes in heart rate or right and left ventricular filling pressures. Similarly, there were no significant changes in coronary sinus flow, $M\dot{V}O_2$ or lactate extraction (Table III).

Effects of Nitroprusside and External Counterpulsation

Figure 4 illustrates the representative effects of nitroprusside alone and combined therapy with nitroprusside and external counterpulsation in a patient with acute myocardial infarction. With nitroprusside alone, there was a slight reduction in arterial pressure from 110/75 to 104/65 mm Hg. The pulmonary capillary wedge pressure decreased from 28 to 18 mm Hg, and cardiac index rose from 1.76 to 2.39 liters/min per m^2. The addition of external counterpulsation during nitroprusside administration (right panel) resulted in restoration of mean diastolic pressure to control levels, a further small increase in cardiac index, and no further change in heart rate or left ventricular filling pressure.

The effects of these two interventions on arterial pressure in all patients are illustrated in Figure 5. Nitroprusside alone produced a reduction in both mean and diastolic arterial pressures. The addition of external counterpulsation did not further alter mean arterial pressure, but greatly augmented peak diastolic pressure and returned mean diastolic pressure to control values (Table IV).

Figure 6 illustrates other hemodynamic effects of these two interventions. Nitroprusside alone produced a significant reduction in pulmonary capillary wedge pressure and an increase in cardiac index. The addition of external counterpulsation to treatment with nitroprusside did not significantly alter any of these variables (Table IV) although in six of nine patients it consistently produced a further slight augmentation of cardiac index. This is illustrated in Figure 7, which shows serial hemodynamic data in one patient during a 3 day period. External counterpulsation was the initial therapy for 1 hour. Following this, nitroprusside was the predominant therapy for several days. At different time intervals, external counter-

TABLE II

Hemodynamic Effects of External Counterpulsation in 11 Patients (means ± standard error of the means)

Group & State	HR	Arterial Pressure (mm Hg) Mean	Arterial Pressure (mm Hg) Mean Diastolic	CI	SWI	SVR	RAP	PCW
No MI (4)								
Control	83 ± 10	93 ± 9	86 ± 7	2.26 ± 0.31	28 ± 4	1900 ± 350	8 ± 1	20 ± 4
EC	83 ± 12	90 ± 10	93 ± 9*	2.33 ± 0.30	28 ± 4	1770 ± 320	9 ± 1	25 ± 7
MI only (2)								
Control	99 ± 4	87 ± 4	81 ± 4	2.23 ± 0.18	25 ± 3	1600 ± 130	10 ± 1	21 ± 2
EC	100 ± 5	96 ± 5	89 ± 6*	2.56 ± 0.22*	32 ± 4*	1560 ± 130	11 ± 2	21 ± 2
MI + shock (5)								
Control	105 ± 7	70 ± 4	66 ± 3	1.81 ± 0.18	14 ± 2	1530 ± 230	8 ± 4	27 ± 5
EC	104 ± 6	74 ± 3	73 ± 5*	2.06 ± 0.27*	17 ± 2*	1470 ± 250	6 ± 3	30 ± 5

* $P < 0.05$, control vs. external counterpulsation.

CI = cardiac index (liters/min per m^2); EC = external counterpulsation; HR = heart rate (beats/min); PCW = pulmonary capillary wedge pressure (mm Hg); RAP = right atrial pressure (mm Hg); SVR = systemic vascular resistance (dynes sec cm^{-5}); SWI = stroke work index (g-m/m^2).

TABLE III

Cardiac Metabolic Effects of External Counterpulsation (EC) in Seven Patients (means ± standard error of the means)

	HR	Mean AP	CI	PCW	CSF	$M\dot{V}O_2$	% Lactate Extraction
C	100 ± 3	87 ± 7	2.40 ± 0.21	24 ± 6	155 ± 31	29 ± 4	29 ± 4
EC	103 ± 3	94 ± 8	2.70 ± 0.26*	27 ± 8	157 ± 31	20 ± 4	20 ± 4

* $P < 0.05$, control vs. external counterpulsation.

AP = arterial pressure (mm Hg); C = control; CSF = coronary sinus flow (ml/min); $M\dot{V}O_2$ = myocardial oxygen consumption (ml/min); other abbreviations as in Table II.

TABLE IV

Hemodynamic Effects of Nitroprusside and External Counterpulsation in Nine Patients (means ± standard error of the means)

		Arterial Pressure (mm Hg)				
	HR	Mean	Mean Diastolic	CI	RAP	PCW
Control	98 ± 6	81 ± 3	71 ± 3	1.71 ± 0.12	11 ± 1	27 ± 3
NP	98 ± 6	73 ± 4*	62 ± 3*	2.25 ± 0.11*	8 ± 1*	19 ± 2*
NP + EC	99 ± 6	73 ± 4	69 ± 4†	2.32 ± 0.10	8 ± 1	19 ± 2

* $P < 0.05$, counterpulsation vs. nitroprusside.
† $P < 0.05$, nitroprusside vs. nitroprusside + external counterpulsation.
NP = nitroprusside; other abbreviations as in Table II.

pulsation was subsequently added to nitroprusside as indicated by the brackets labeled EC. External counterpulsation by itself, and when added to nitroprusside therapy, always produced a slight further increase in cardiac index. The reduction in pulmonary capillary wedge pressure and rise in cardiac index produced by administration of nitroprusside were abruptly reversed when the drug was discontinued and promptly returned when it was reinstituted (on 7-14 for example). There was a gradual rise in cardiac index over the first 3 days, which is characteristic of patients with severe pump failure who subsequently survive after nitroprusside therapy.[5]

Clinical course: There were no perceptible changes in the clinical condition of the patients with external counterpulsation alone, but administration of nitroprusside usually resulted in clinical improvement. This was manifested as a decrease in dyspnea as the pulmonary capillary wedge pressure was reduced and a slight warming of the limbs as cardiac output increased. These clinical signs were quickly reversed when the nitroprusside therapy was discontinued, which prompted a continuous (1 to 5 days) infusion of nitroprusside in some patients, particularly to control dyspnea.

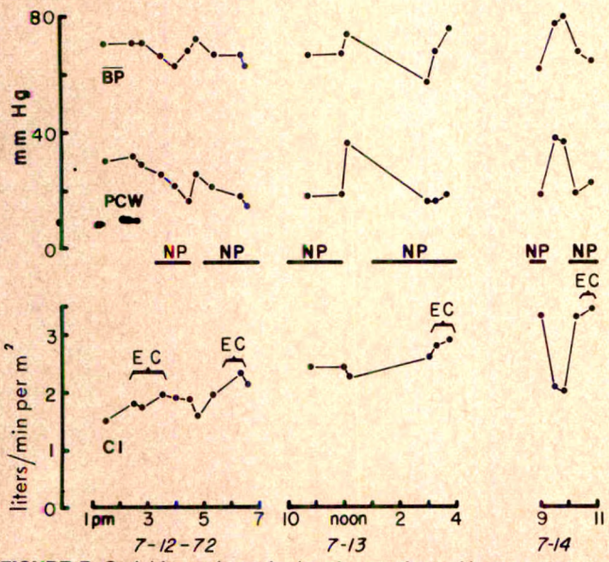

FIGURE 7. Serial hemodynamic data in a patient with severe pump failure after acute myocardial infarction. Mean arterial pressure ($\overline{BP}$), pulmonary capillary wedge pressure (PCW) and cardiac index (CI) are plotted as a function of time with representative samplings of 3 successive days included in the graph. The **solid line** (NP) indicates each period of nitroprusside infusion. The brackets labeled EC indicate each 1 hour period of external counterpulsation.

Although the number of patients in our study is too small to make conclusions about the effect of combined therapy on mortality (Table I), recent studies[5] with the use of nitroprusside alone have suggested a reduction in the mortality rate of cardiogenic shock from 85 to 40 percent.[5]

Discussion

Clinical use of invasive circulatory assist devices (intraaortic balloon) has produced beneficial hemodynamic effects in some patients, although the final result is often dependent on the initial degree of myocardial damage.[1] Because the insertion and operation of these devices require a specially trained team their application has been restricted to major research centers. Therefore, rapidly applicable *noninvasive* application of these same principles of circulatory assistance (systolic unloading and diastolic augmentation) is an attractive goal for physicians who do not have ready access to such centers.

Previous studies with drugs that decrease peripheral vascular resistance, such as phentolamine or nitroprusside, have suggested that beneficial hemodynamic effects can be obtained by systolic unloading in this manner.[2–5] Our findings also confirm that nitroprusside can produce a decrease in left ventricular filling pressure together with an increase in cardiac output and a reduction in myocardial oxygen demands.[5] The potential drawback to this therapy appears to be the reduction in diastolic perfusing pressure, which might compromise coronary blood flow, particularly if the level of arterial pressure is initially low. Accordingly, the simultaneous application of external counterpulsation to maintain diastolic perfusing pressure is an attractive concept. The critical level of coronary perfusing pressure has not been determined in man, and indeed is probably critically dependent on the degree of obstruction of the coronary circulation in each individual. Nevertheless, in most patients with pump failure, it is likely that aug-

mentation of diastolic pressure may protect against any potentially deleterious effects of nitroprusside infusion.

In this study, the hemodynamic effects of external counterpulsation consisted of a 7 mm Hg increase in mean diastolic pressure and a 14 percent rise in cardiac index. When external counterpulsation was added to nitroprusside therapy, diastolic pressure was returned to control levels, and in six of nine patients there was a further small rise in cardiac index. Thus, the combination of these two therapies appeared to be better than either one alone, although the predominant beneficial hemodynamic effects were produced by nitroprusside. Nitroprusside is valuable in patients with filling pressures greater than 15 mm Hg.[5] In patients with smaller initial filling pressures, nitroprusside caused tachycardia, accompanied by no change or a decrease in cardiac output.[5]

Clinical applications: In patients who arrive at the hospital with reduced arterial pressure, the immediate application of external counterpulsation may be a beneficial first step in increasing or at least maintaining vital coronary perfusion of ischemic myocardium. Once diastolic pressure has been augmented, it may then be possible to add nitroprusside therapy to reduce filling pressure, raise cardiac index and reduce myocardial oxygen consumption.

This combination therapy will also be beneficial for patients who have associated mitral regurgitation due to papillary muscle dysfunction. Nitroprusside[10] and intraaortic balloon counterpulsation[11] have each been effective in patients with mitral regurgitation, presumably because of their ability to produce systolic unloading. Diastolic augmentation may also help, however, if arterial pressure is reduced.

Drawbacks of external counterpulsation: Potential limitations of external counterpulsation include the discomfort that patients experience at high levels of pumping pressures for long periods of time (more than 2 to 3 hours). In most patients this discomfort necessitates application of the device in a periodic manner or at reduced pumping pressures that may diminish the degree of diastolic augmentation. External counterpulsation appears to be totally ineffective in patients with severe peripheral vascular disease. Local abrasions on the legs occurred in a few patients, but could be prevented by judicious placement of cotton padding. The use of external counterpulsation is also limited when there are tachyarrhythmias (rates higher than 150/min) or other serious rhythm disturbances that make it difficult for the timing and mechanical elements to follow the electrocardiographic signal. In general, however, the Cardiassist is easy to apply, reliable and immediately available for patients when they arrive at the hospital.

In summary, it appears possible to apply the principles of invasive circulatory assistance in a relatively noninvasive manner to patients with severe pump failure. The speed and ease of application may provide certain advantages in early reversal of the vicious cycle of increasing hypotension and poor coronary perfusion associated with cardiogenic shock. Although the major hemodynamic advantages appear to be related to systolic unloading with nitroprusside, the potential importance of maintaining arterial diastolic pressure is obvious and warrants continued investigation. The application of external compression to the lower limbs is patently a less effective means of altering aortic root dynamics than use of a displacement device positioned more proximally in the central arterial tree.[1] Nevertheless, the addition of external counterpulsation appears to produce sustaining levels of diastolic arterial support in seriously ill patients.

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Prognostic Indexes in Acute Myocardial Infarction Complicated by Shock

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The predictive value of selected hemodynamic, metabolic, respiratory and renal variables was assessed in 29 patients with acute myocardial infarction complicated by shock. Arterial blood lactate was the most reliable variable individually and in combination with other variables. Individual measurements of blood flow were more reliable than measurements of blood pressure.

Prognostic indexes were derived using discriminant function analysis. Indexes based on current values of the variables were more useful than those utilizing repetitive values. Nonlinear combinations of arterial pressure and flow measurements did not provide a significant improvement over standard linear combinations. The use of the prognostic indexes provides an objective basis for assessing the severity of the patient's illness and his response to treatment.

In previous studies of prognostic indicators in patients with acute myocardial infarction and shock, the value of hemodynamic variables as predictors of survival was examined.[1] On the basis of data from 20 patients, stroke index emerged as the best single predictor. When two variables were combined in a linear manner, it was possible to increase the reliability of predicting survival. The best combination of two hemodynamic variables was stroke index and diastolic pressure. Inclusion of additional variables did not significantly improve reliability. In a later study[2] on patients with drug overdose, metabolic and respiratory variables were evaluated in addition to the hemodynamic variables. In this group of patients, systolic pressure was the best single predictor of survival, and systolic pressure and arterial pH was the best combination of two variables. Other variables, particularly arterial blood lactate levels, could be combined with systolic pressure to give comparable reliability.

These indexes were derived from single sets of concurrent measurements. However, it seemed reasonable to assume that the previous course of the patient might influence the prognosis. Accordingly, sequential sets of measurements were used to derive an accumulative prognostic index.[2] In patients with drug overdose, this index provided a more meaningful assessment of patient status and prognosis than that provided by concurrent measurements alone.

In this study of 29 patients with myocardial infarction and shock, metabolic, respiratory and renal variables were examined in addition to hemodynamic variables to determine their predictive value. Prognostic indexes based on groups of variables were derived. The efficacy of accumulative prognostic indexes also was evaluated.

Methods

Clinical Material

Twenty-nine patients with an acute myocardial infarction subsequently complicated by unequivocal clinical manifestations of shock were studied. In-

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TABLE I

Clinical Features in 29 Cases

Case no.	Age (yr) & Sex	History			Symptoms			Other Conditions	Outcome
		MI	Hy	CHF	CP	Dy	Sy		
1	51M	+	...	...	...	...	...	Pulmonary emphysema	S
2	64M	...	+	+	+	+	...		D
3	48M	...	...	...	+	...	...		S
4	75M	...	...	...	+	...	...	Cerebral vascular disease; duodenal ulcer	D
5	76F	...	...	...	+	...	...		D
6	58M	+	+	+	...	+	...	Diabetes mellitus	D
7	74F	+	+	+	+	...	+	Cerebral vascular disease	D
8	71M	...	...	...	+	...	...		D
9	62F	...	+	...	+	...	...		D
10	70F	...	+	...	...	+	+		D
11	56M	+	...	...	+	...	...	Epilepsy, grand mal	S
12	47M	...	...	...	+	+	...		S
13	75F	+	...	...	+	+	...		D
14	67M	...	+	+	+	+	...		D
15	69F	+	...	...	+	+	...	Diabetes	D
16	62M	...	...	...	+	+	...	Pulmonary emphysema	S
17	63M	...	...	...	+	...	+		S
18	74M	...	...	...	+	...	+		D
19	54M	+	...	+	+	+	...		D
20	70F	+	...	...	...	...	...		D
21	50M	+	...	...	...	...	...	Previous stroke	D
22	58M	...	...	...	+	...	...	Peripheral vascular disease	D
23	68M	...	...	+	...	...	...	Diabetes mellitus	D
24	68M	+	...	...	...	...	+	Diabetes mellitus	D
25	57M	+	...	...	+	+	+	Previous stroke; peptic ulcer	D
26	84M	...	...	...	+	...	...		D
27	65M	+	...	...	+	...	...	Gout	D
28	53M	...	...	...	...	+	...	Diabetes mellitus	D
29	51M	+	...	...	...	+	...	Pulmonary emphysema	S

CHF = previous congestive heart failure; CP = chest pain; D = died; Dy = dyspnea; Hy = hypertension; MI = previous myocardial infarction; S = survived; Sy = syncope.

cluded were 22 men and 7 women ranging in age from 47 to 84 (median 64, mean 63.4) years. Seven of the patients recovered from the initial episode. On the patients' admission to the critical care ward, systolic pressure determined by the auscultatory technique was less than 80 mm Hg, the sensorium clouded, the skin clammy and urinary output less than 20 ml/hour. The clinical features are summarized in Tables I and II and the hemodynamic, respiratory and metabolic measurements in Table III. The electrocardiogram showed Q waves and S–T and T wave changes characteristic of acute transmural myocardial infarction in all but one patient. Serum glutamic oxaloacetic transaminase and lactic dehydrogenase were significantly increased in every patient. The heart was examined at autopsy in 13 patients, including the patient who had equivocal electrocardiographic changes. Acute transmural myocardial infarction with extensive muscle necrosis was confirmed in each case.

Patients were observed in the critical care ward for an average of 28 hours. The initial set of measurements was taken after discontinuation of treatment with vasoactive drugs. Subsequent measurements were obtained while patients were treated with standard therapeutic agents, including vasoactive drugs, cardiac glycosides and oxygen, at the discretion of the attending physician. The final set of observations consisted of the last measurements obtained before transfer of the patient to another ward, or before death exclusive of the agonal period.

TABLE II

Survival by Clinical Features

Clinical Features	With		Without	
	no.	Percent Survived	no.	Percent Survived
Acute myocardial infarction				
Anterior	20	20	9	33
Inferior	9	33	20	20
Chest pain	19	26	10	20
Dyspnea	12	25	17	24
Syncope	6	17	23	26
Previous myocardial infarction	13	23	16	25
Previous hypertension	7	0	22	32
Previous congestive heart failure	6	0	23	30

Hemodynamic, Metabolic and Respiratory Data

Twenty-two variables were routinely measured at intervals ranging from every 5 minutes to every 4 hours (Table III). Two variables, plasma volume index and red cell index, were measured at intervals of 12 to 24 hours. In

TABLE III

Initial and Final Mean Values by Survival

Variable	Initial Values			Final Values		
	S	D	*P* Value	S	D	*P* Value
SP (mm Hg)	94	84	...	102	82	<0.05
MAP (mm Hg)	74	60	<0.05	75	57	<0.05
DP (mm Hg)	61	49	<0.05	61	46	<0.05
HR (beats/min)	94	93	...	86	94	...
RT (°C)	38.0	37.5	...	38.1	37.4	...
MVP (mm Hg)	7.2	10.7	...	8.9	9.9	...
CI* (liters/min per m^2)	1.4	1.3	...	2.4	1.5	<0.05
SI (ml/beat)	16	16	...	32	19	<0.01
AT (sec)*	11.7	13.7	...	9.7	14.9	<0.05
MCT (sec)*	28.8	35.5	...	21.4	33.6	<0.05
UO (ml/hr)	77	43	...	93	20	<0.01
PVI (ml/kg)*	40	41	...	54	42	<0.05
RCI (ml/kg)*	26	23	...	20	21	...
Hgb (g/100 ml)	15.3	13.4	...	12.3	12.0	...
Hct (%)	48	41	<0.05	34	37	...
pHa (units)	7.43	7.34	...	7.44	7.36	...
PaO_2 (mm Hg)	114	126	...	134	135	...
SaO_2 (%)	94	95	...	98	96	...
$PaCO_2$ (mm Hg)	46	35	<0.05	45	37	...
LAC (millimoles)*	1.99	5.85	<0.01	1.23	7.30	<0.005
PVR (dynes sec cm^{-5})	2417	1826	...	1322	1721	...
CW (g-m)	2575	2114	...	4639	2265	<0.01
CBV (liters)	1.28	1.45	...	1.63	1.45	...
SW (g-m)	28	23	...	57	25	<0.005

* Values shown are antilogs of the mean logarithmic values.

AT = appearance time; CBV = central blood volume; CI = cardiac index; CW = cardiac work; D = died; DP = intraarterial diastolic pressure; Hct = arterial hematocrit; Hgb = arterial hemoglobin; HR = heart rate; LAC = arterial blood lactate; MAP = mean arterial pressure; MCT = mean circulation time; MVP = mean central venous pressure; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; pHa = arterial pH; PVI = plasma volume index; PVR = peripheral vascular resistance; RCI = red cell index; RT = rectal temperature; S = survived; SaO_2 = arterial oxygen saturation; SI = stroke index; SP = intraarterial systolic pressure; SW = stroke work; UO = urinary output.

some patients, individual variables were not measured because of technical considerations. For each patient, the first measurement of each variable was called the "initial" value and the last measurement before death or discharge, the "final" value. Values for arterial systolic and diastolic pressure, mean arterial pressure, mean central venous pressure, heart rate, peripheral vascular resistance, cardiac index, cardiac work, mean circulation time, appearance time, central blood volume and stroke index were obtained by previously described techniques.[3–5] Hourly urinary output was measured with the use of an automated urinometer attached to an indwelling urethral catheter. Rectal temperature was measured by means of thermistor probes.[6] Plasma volume was determined with ^{131}iodine- or ^{125}iodine-tagged iodinated serum albumin (RISA) and red cell mass with ^{51}chromium-tagged red blood cells.[7] Both of these values were standardized by weight to obtain plasma volume index and red cell index. Laboratory procedures used for measurement of hematocrit, hemoglobin, arterial pH, partial pressures of carbon dioxide, oxygen saturation and lactate have been described previously.[8,9]

Results

The outome with respect to specific clinical features is summarized in Table II. There was no statistically significant difference in survival rate for any of the clinical factors listed in Table II ($P > 0.10$). However, there were no survivors among patients with previous hypertension or congestive heart failure.

The statistical techniques used in our study assume that the values of the measured (continuous) variables follow normal distributions. To test the validity of this assumption, the empirical distribution of each variable was tested for normality by means of the chi-square goodness-of-fit test. All but six variables, cardiac index, appearance time, mean circulation time, plasma volume index, red cell index and arterial blood lactate, showed approximate normal distributions. Taking the logarithm of these variables produced approximate normal distributions.

Analysis of Single Variables

The *t* test was used to compare the mean values of the initial and final measurements in patients who survived the infarction with initial and final measurements in patients who died (Table III). Among the initial variables, arterial blood lactate, mean arte-

rial pressure, intraarterial diastolic pressure, arterial hematocrit and partial pressure of carbon dioxide showed a significant mean difference ($P < 0.05$). The final values of arterial hematocrit and partial pressure of carbon dioxide were not significant, although nine additional variables showed significant mean differences.

This analysis only demonstrates whether there were significant mean differences between patients who survived and patients who died. However, our interest lies mainly in determining the ability of each variable to predict whether the patient will survive his critical illness. To this end, a reference value was determined for each variable so that a patient would be classified as a survivor if his measured value exceeded the reference value. For certain variables, arterial blood lactate and appearance and mean circulation times, for example, a measured value of less than the reference value was indicative of survival. The procedure used to calculate the reference values is as follows[10]:

$$\text{Reference value} = (\text{mean value for survivors} + \text{mean value for nonsurvivors}) / 2$$

The measure of discriminating ability of a given variable is the Mahalanobis distance, which is defined as:

$$D^2 = (\text{mean value for survivors} - \text{mean value for nonsurvivors})^2 / \text{pooled variance}$$

where the pooled variance is calculated as the weighted average of the variances for survivors and patients who died. The Mahalanobis D^2 is a measure of the "distance" between the populations of survivors and nonsurvivors. The larger the value of D^2, the easier it is to correctly predict the patient's outcome. The percent probability of correct prediction, referred to as the reliability, is estimated as 100 times the area under the standard normal curve to the left of D/2.

Initial and final reference values and reliabilities were computed for each variable (Table IV). The sign preceding a reference value indicates the region in which survival is predicted. Thus, for example, a patient is predicted to survive if his initial systolic pressure is greater than 89 mm Hg; otherwise, he is predicted to die. Using this procedure of classification based on intraarterial systolic pressure alone, one would expect a correct prediction in 60 percent of cases. Among the initial values, arterial blood lactate was the most reliable single predictor (77 percent), followed by arterial hematocrit, partial pressure of carbon dioxide, mean arterial pressure and intraarterial diastolic pressure. The reliability of individual final values was generally greater than the corresponding reliability of initial values. Again, final values for arterial blood lactate were the most reliable (85 percent), followed by those for stroke work, urinary output, cardiac work and stroke index.

Analysis of Sets of Variables

The univariate analysis provides a measure of the prognostic ability of each variable separately. The statistical technique of discriminant function analysis[10] offers a method for combining values of several variables to predict

TABLE IV

Reference Values and Reliability Rates of Single Variables in Predicting Survival

	Initial Values		Final Values	
Variable	Reference Value	Reliability (%)	Reference Value	Reliability (%)
SP	>89	60	>91	68
MAP	>67	69	>66	71
DP	>55	68	>53	71
HR	>93	50	<90	55
RT	>37.7	57	>37.7	59
MVP	<8.9	63	<9.4	54
CI	>1.4	50	>1.8	70
SI	>16	51	>25	73
AT	<13	53	<12	72
MCT	<31.8	61	<26.8	71
UO	>60	59	>56	78
PVI	>41	51	>48	70
RCI	>24	52	<21	53
Hgb	>14.3	69	>12.1	51
Hct	>44	75	<35	57
pHa	>7.38	64	>7.40	64
$PaCO_2$	>41	71	>41	62
SaO_2	<94	53	>97	57
PaO_2	<120	52	<134	50
LAC	<3.41	77	<2.99	85
PVR	>2140	61	<1522	58
CW	>2345	58	>3123	77
CBV	<1.36	56	>1.54	56
SW	>26	58	>41	82

Abbreviations and units as in Table III.

survival in an optimal way. Briefly, if one denotes the variables by $X_1, \ldots, X_k$, one forms the following linear discriminant function

$$Z = a_1X_1 + a_2X_2 + \ldots + a_kX_k$$

and can classify the patient as a survivor if Z is greater than the reference value. This discriminant function Z is derived by the addition of weighted values of the available variables. The weights $a_1, \ldots, a_k$ are chosen so that the probability of correct prediction is maximized. The reference value for Z is calculated as the average of the mean Z values for survivors and nonsurvivors. The Mahalanobis distance and reliability values are also readily estimated.[10] In this study, a stepwise discriminant analysis program[11] was used. The program first selected the single variable with the greatest reliability. The variable giving the greatest reliability when combined with the first variable was then selected, and so forth, until inclusion of additional variables did not significantly improve prediction.

Initial and final values were analyzed separately. The analysis was performed twice: once for the total group of 29 patients, in which case arterial blood lactate was not included as one of the variables, and again for a group of 24 patients whose arterial blood lactate values were available and were used in the analysis. Measurements of rectal temperature, urinary output, plasma volume index, red cell index, arterial hemoglobin, arterial hematocrit, arterial oxygen saturation and partial pressure of oxygen were not included in this phase of the analysis since only a few pa-

TABLE V

Prognostic Reliability of the Best Linear Combinations of Variables

Initial Values		Final Values	
Combination	Reliability (%)	Combination	Reliability (%)
A. Excluding Lactate (29 patients)			
$PaCO_2$, pHa	78	SI, DP	84
$PaCO_2$, DP	78	SI, MAP	81
$PaCO_2$, MAP	77	SI, SP	78
MVP, MAP	77		
MVP, DP	76		
B. Including Lactate (24 patients)			
LAC, $PaCO_2$	82	LAC, $PaCO_2$	89
LAC, DP	80	LAC, SI	88
		LAC, MVP	87

Abbreviations as in Table III.

TABLE VI

Final Discriminant Functions and Reference Values for the Best Combinations of Two Variables

Combination	Discriminant Function	Reference Value
Metabolic-respiratory	0.12188 $PaCO_2$ — 5.98884 log LAC	2.16062
Metabolic-hemodynamic	0.09724 SI — 5.11412 log LAC 0.24926 CVP — 7.1940 log LAC	0.15818 —0.98032
Hemodynamic	0.1214 DP + 0.1523 SI	10.3263

Abbreviations as in Table III.

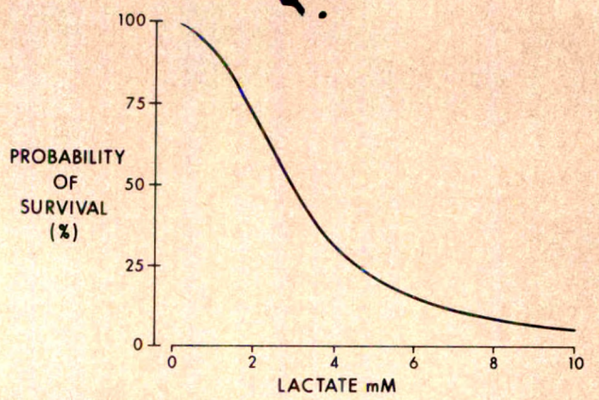

FIGURE 1. Probability of survival based on arterial blood lactate.

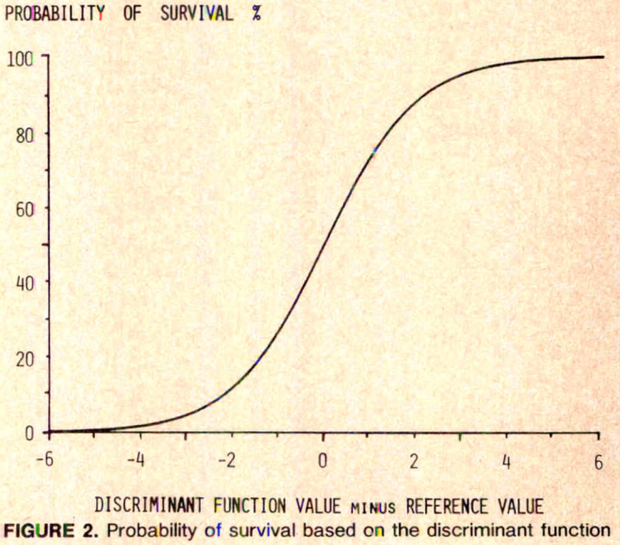

FIGURE 2. Probability of survival based on the discriminant function and reference value.

tients had measurements of all these variables. Because cardiac work and stroke work are derived nonlinear variables, they were also considered separately.

Initial values: Exclusive of arterial blood lactate, partial pressure of carbon dioxide in arterial blood had the greatest reliability of a single variable when initial values were used. When other single variables were combined with partial pressure of carbon dioxide, arterial pH contributed most to predicting survival. This improvement in reliability was statistically significant ($F = 4.9$, degrees of freedom 1, 26; $P < 0.05$). Of all the remaining variables, intraarterial diastolic pressure contributed most to this combination; however, this contribution was not statistically significant ($P > 0.10$). When arterial blood lactate was included, this variable was the most reliable. The variable that best contributed to arterial blood lactate was partial pressure of carbon dioxide. The improvement was of borderline statistical significance ($F = 3.9$, degrees of freedom 1, 21; $P < 0.06$). Other combinations of two variables that gave comparable reliability are shown in Table V.

Final values: Exclusive of arterial blood lactate, stroke index was the most reliable single variable when final values were used (Table IV). When other single variables were added, intraarterial diastolic pressure contributed most significantly ($F = 9.1$, degrees of freedom 1, 26; $P < 0.01$). Inclusion of additional variables did not significantly improve the reliability of prediction. When arterial blood lactate was included it was the best single predictor. Partial pressure of carbon dioxide was the only other variable that contributed to the reliability of arterial blood lactate. As with the initial values, this contribution was of borderline significance ($F = 3.7$, degrees of freedom 1, 21; $P < 0.07$). Other combinations of two variables that gave comparable reliability are shown in Table V.

Probability of Survival

To predict whether a patient will survive an acute episode, the discriminant function based on the final rather than the initial value is used, since the final values of survivors are more clearly separated from

those of patients who died. Instead of the discriminant function value, a clinically more meaningful assessment of the patient's status may be expressed in terms of the probability of survival, based on the value of a given variable or discriminant function. The probability of survival as a function of the value of arterial blood lactate is plotted in Figure 1. Thus, for a patient with an arterial blood lactate value of 2 millimoles, the likelihood of survival would be 73 percent. The formulas of the discriminant functions and the reference values, based on the best combinations of two variables, are shown in Table VI. For any discriminant function, the probability of survival may be read directly from the ordinate in Figure 2 by entering the difference between the reference and the discriminant function values on the abscissa. The probability of survival at any given time is referred to as the momentary prognostic index.

Accumulative Prognostic Indexes

The value of the discriminant function computed from current measurements does not necessarily reflect the previous course of the patient's illness. A more comprehensive assessment of the patient's status might take into account previous values of the discriminant function. For each of the 29 patients, intraarterial diastolic pressure and stroke index were used to compute the final discriminant function every 1 to 4 hours. The values of this final discriminant function were used in each patient to obtain the least-squares estimates of the intercept (a) and slope (b) as a function of time. This procedure was also used in 24 patients for the values of the final discriminant function based on arterial blood lactate, arterial blood lactate and partial pressure of carbon dioxide, and arterial blood lactate and stroke index. None of the mean slopes showed a significant difference between survivors and patients who died. Only the mean intercept of the final discriminant function based on arterial blood lactate and partial pressure of carbon dioxide reflected a significant difference. Inclusion of the trends of the final discriminant function did not provide significant additional predictive information. For this reason, no accumulative prognostic indexes were derived.

Nonlinear Prognostic Indexes

The discriminant functions listed in Table VI are all linear (additive) combinations of variables. Clinical experience has indicated that nonlinear combinations of data also may be useful. Such nonlinear combinations may be the products or ratios of certain variables, such as cardiac work, stroke work, peripheral vascular resistance and central blood volume (Table III). Among these, the final value of stroke work was the most reliable predictor of survival (Table IV). The relatively high level of reliability of this nonlinear combination motivated examination of other combinations of arterial pressure and blood flow. The formula, cardiac work = 13.6 × mean arterial pressure × cardiac output, was modified by using intraarterial systolic or diastolic pressure instead of mean arterial pressure, or cardiac index instead of cardiac output, or both. In addition to these modifications, six additional nonlinear combinations were obtained by dividing by heart rate. Among these combinations, intraarterial diastolic pressure × stroke index and intraarterial diastolic pressure × stroke volume, each provided the greatest reliability (85 percent), followed by mean arterial pressure × stroke index (83 percent). These combinations of pressure and flow measurements might be compared to stroke work = 13.6 × mean arterial pressure × stroke volume. However, they do not have specific physiologic designations, and their reliability is not significantly greater than that of the standard stroke work.

Discussion

In earlier studies in this unit on patients with acute myocardial infarction and shock, stroke index and intraarterial diastolic pressure provided the best combination of hemodynamic variables for predicting survival.[1] In a later study[2] on patients with drug overdose, an accumulative prognostic index was developed that took into account sequential changes in hemodynamic, metabolic and respiratory variables. In this study on an enlarged group of patients with myocardial infarction, selected metabolic, respiratory and renal variables were analyzed to determine whether they contribute to the information available from the hemodynamic variables alone. The sequential changes in these variables also were examined to determine whether an accumulative prognostic index could be developed for this group of patients.

Recent studies have suggested that measurements of pulmonary arterial wedge and left ventricular pressures may provide valuable prognostic information on the status of the left ventricle.[12–16] Measurements of these variables were available in several of the more recent patients, and the observations appear to indicate the value of such measurements. However, the data were not sufficient to warrant detailed statistical analysis. Among the hemodynamic variables measured in all patients, stroke index again emerged as the best single prognostic variable. Other measurements of flow, appearance time and mean circulation time also were more reliable than measurements of arterial pressure. When metabolic, respiratory and renal variables were included, arterial blood lactate emerged as the best individual prognostic variable. Urinary output was better than any single hemodynamic or respiratory variable. These findings are in contrast to those in patients with drug overdose, in whom measurements of arterial pressure were the most reliable followed by measurements of arterial pH and arterial blood lactate. In patients with drug overdose, measurements of blood flow were not significant predictors of survival.

The best prognostic indexes of survival in cardiogenic shock: The linear (additive) combination of arterial blood lactate with either partial pressure of carbon dioxide, stroke index or mean central venous pressure provided the greatest reliability in pre-

dicting survival in patients with myocardial infarction complicated by shock. The value of the partial pressure of carbon dioxide can be readily altered by changing the minute volume in a patient on a ventilator. For this reason, it may be preferable to use values of stroke index or mean central venous pressure in combination with those for arterial blood lactate. Among hemodynamic variables, the combination of stroke index and intraarterial diastolic pressure again provided the greatest reliability. In contrast to these findings, among patients with drug overdose, the combination of intraarterial systolic pressure with either arterial pH or arterial oxygen saturation produced the greatest reliability.

Another important difference between patients with myocardial infarction and those with drug overdose relates to the value of accumulative prognostic indexes. Whereas the accumulative prognostic index proved to be a valuable tool in the patients with drug overdose, it was not as helpful as the prognostic index based on only current values (momentary prognostic index) in patients with myocardial infarction and shock. The explanation for this lies in the different courses of the two groups of patients. In patients with drug overdose, the survivors and patients who died showed clearly divergent trends; among patients with myocardial infarction, there was no consistent trend in patients who died. However, the momentary prognostic index for patients with myocardial infarction does reflect the severity of the patient's condition and serves as a valuable prognostic indicator.

This prognostic index is derived solely from measured (continuous) variables. Inclusion of discrete variables, such as the clinical features listed in Table II, might be expected to improve reliability of such indexes.[17] For example, there were no survivors among patients with previous hypertension or congestive heart failure. Nevertheless, previous hypertension was not a significant factor in predicting survival in our group of 29 patients. This finding indicates the need for a larger number of patients when discrete variables are analyzed.

Although the linear (additive) discriminant function is usually the best predictive combination of variables, it is possible that some nonlinear combinations, such as those derived from products and ratios of variables, might provide greater reliability. For example, stroke work, which is a nonlinear combination of mean arterial pressure, cardiac output and heart rate, provides a high level of reliability. The nonlinear hemodynamic combinations that were considered did not yield a significant improvement over the linear combinations of hemodynamic variables in the reliability of predicting survival.

Depending on the availability of the measured variables, combinations of hemodynamic, respiratory and metabolic measurements may be selected to assess the patient's status at any given time. The prognostic indexes are given in Table VI. These indexes provide a basis for objectively evaluating the severity of a patient's illness before and after any given therapeutic intervention.

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Mechanism and Significance of Widened QRS Complexes During Complete Atrioventricular Block in Acute Inferior Myocardial Infarction

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Twelve of 35 consecutive patients admitted with complete atrioventricular (A–V) block complicating acute inferior myocardial infarction manifested widened QRS complexes. The escape beats had the pattern of left bundle branch block in four patients, right bundle branch block in five patients and both left and right bundle branch block in three patients.

His bundle recordings in five patients with escape beats that had a left bundle branch block configuration revealed a His bundle potential preceding the widened QRS complex at His–V intervals of 45 to 60 msec. Bradycardia-dependent left bundle branch block was demonstrated in two patients by His bundle pacing. In three patients the conducted beats had a left bundle branch block configuration after critical lengthening of the R–R interval during second degree A–V block before or after the episode of complete A–V block. In six patients whose escape beats had a right bundle branch block configuration, His bundle recordings did not reveal a His bundle potential preceding these beats.

Our observations suggest that widened QRS complexes with a left bundle branch block configuration could be due to an A–V junctional escape rhythm with phase 4 left bundle branch block. Alternatively in association with a right bundle branch block configuration it is possible that the widened QRS complexes represent a ventricular or fascicular escape rhythm.

Two of 12 patients with widened QRS complexes died. There were no significant differences in immediate mortality, 6 month mortality or mean peak serum glutamic oxaloacetic transaminase (SGOT) values between patients with narrow and widened QRS complexes. This finding suggests that widened QRS complexes during complete A–V block in acute inferior myocardial infarction have no prognostic significance.

Atrioventricular (A–V) conduction disturbances associated with acute inferior myocardial infarction are generally located in the A–V node when occlusion occurs proximal to the origin of the A–V nodal artery.[1-8] In 90 percent of cases this artery is a branch of the right coronary artery.[9] During complete A–V block the escape pacemaker below the site of block usually produces narrow QRS complexes.[1-8] Prolongation of QRS duration during complete A–V block in inferior myocardial infarction is considered to be of prognostic significance and to be associated with a high mortality rate.[6,7,10,11] It has been suggested that in these circumstances A–V block originates below the node.[12,13]

In this study we attempted to determine the frequency, prognostic significance, mechanism and site of origin of widened QRS complexes

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TABLE I

Summary of 12 Cases with Widened QRS Complexes During A–V Block

Case no.	Age (yr) & Sex	QRS Complex		Heart Rate (beats/min)	His–V Interval (msec)		Follow-Up Period (months)
		Type	Duration (sec)		WQRS	NQRS	
1	72M	LBBB	0.14	55	50	50	6
		RBBB	0.12	45	nH		
2	76M	LBBB	0.14	45	45	45	6
		RBBB	0.16	55	nH		
3	67M	RBBB	0.14	55	nH	50	6
4	75M	LBBB	0.12	60	45	40	7
		RBBB	0.12	50	nH		
5	67M	LBBB	0.14	70	60	60	8
6	62M	RBBB	0.12	50	nm	nm	8
7	59M	RBBB	0.12	50	nm	nm	8
8	69M	LBBB	0.16	45	nm	nm	9
9	58M	RBBB	0.14	60	nH	45	10
10	63M	LBBB	0.16	45	45	45	17
11	73F	LBBB	0.16	60	nm	nm	Died 1st week
12	78M	RBBB	0.14	40	nH	40	Died 4th week

LBBB = left bundle branch block configuration; nH = QRS not preceded by His bundle potential; nm = HV interval not measured; NQRS = narrow QRS complexes in escape or conducted beats, or both; RBBB = right bundle branch block configuration; WQRS = widened QRS complexes in escape beats.

during complete A–V block in the setting of acute inferior myocardial infarction.

Material and Methods

The subjects were 225 patients admitted consecutively to the coronary care unit from February 1972 to July 1973 because of acute inferior myocardial infarction. All patients were admitted within 24 hours after the onset of symptoms, and the mean hospital arrival time was 4 hours. The diagnosis of acute infarction was based on a typical history of chest pain correlated with the appearance of diagnostic Q waves and characteristic serial changes in serum enzymes. In all patients with acute myocardial infarction, continuous electrocardiographic monitoring was performed. In several of these patients the electrocardiographic data were stored on magnetic tape. A 14 lead electrocardiogram with seven leads recorded simultaneously was obtained twice a day during the first 5 days, and additional electrograms were taken as necessary.

The location of infarction was defined according to the criteria of Lipman and Massie.[14] The group of patients with inferior infarction included those with the characteristics of diaphragmatic or posterior wall infarction (or both) with or without lateral wall involvement. The diagnosis of left and right bundle branch block was based on the criteria of the New York Heart Association.[15] High degree A–V block was defined as the presence of either second or third degree A–V block. Temporary pacing was instituted in high degree A–V block combined with cardiac failure, ventricular rates of less than 50/min or ventricular irritability.

In 8 of 12 patients with acute inferior myocardial infarction manifesting widened QRS complexes in the presence of complete A–V block, the sites of A–V block and escape mechanisms were studied by His bundle recordings. Informed consent was given by each of these patients. In one of the patients not catheterized, the widened QRS pattern has disappeared; diagnostic facilities were not available in the other three cases. During this procedure, three electrode catheters were passed through the femoral vein by the Seldinger technique. A tripolar electrode catheter was used to record the His bundle electrogram,[16] a bipolar catheter was positioned in the right ventricular apex for stimulation and a third unipolar catheter was used to record the intracavitary atrial complex. The site of block during complete A–V block was defined according to the criteria of Hecht and Kossmann.[17] The site was considered to be located in the A–V junction if, in the presence of a normal His–V interval, no P wave was followed by a His bundle potential. The A–V junction was defined to include the A–V node and the nonbranching part of the His bundle. Normal values for the His–V interval in our laboratory are 35 to 55 msec.

Two patients underwent stimulation of the His bundle. All eight patients were restudied by His bundle recordings, two during second degree A–V block and six after 1:1 A–V conduction had resumed. Four patients in the latter group were restudied at least 6 weeks after the onset of infarction. At that time the functional and effective refractory periods of the A–V node were also determined using the single test stimulus method during atrial pacing.[18]

Electrocardiographic leads I, II, III, V_1 and V_6, the unipolar intraatrial lead and the His bundle lead were recorded simultaneously, the latter with use of an Elema amplifier type EMT 12. The electrocardiograms were recorded on an eight channel high frequency direct-writing Elema recorder.

After discharge, all patients were followed up at intervals of 3 months. The significance of differences between mean peak values for serum glutamic oxaloacetic transaminase was tested by the Student *t* test. A chi square test was used to test the significance of differences in mortality rate.

Results

The hospital mortality rate in the 225 patients with acute inferior myocardial infarction was 11 percent. The mean age of all patients was 62 years, and

TABLE II

Mean Age, Mean Peak SGOT Values, Hospital and 6 Month Mortality Data of 35 Patients with A–V Block

	Patients (no.)	Mean Age (yr)	Mean Peak SGOT		Mortality	
			Units	Log*	Hospital	6 Months
Narrow QRS	23	63.2 (±9.4)	128	2.06 (±0.22)	5/23	1/15†
Widened QRS	12	68.2 (±6.7)	138	2.11 (±0.16)	2/12	0/10
P value		NS		NS	NS	NS

* For statistical analysis the logarithms of SGOT were used.

† These figures were related to patients who were followed up for at least 6 months.

Figures in parentheses indicate standard deviation; NS = not significant, $P < 0.10$; SGOT = serum glutamic oxaloacetic acid.

the mean peak value for SGOT was 97 international units (IU). Complete A–V block developed in 35 (15.5 percent) of the total group. The mean age of these patients was 65 years, and the mean peak value for SGOT was 132 IU. Seven (20 percent) of these 35 patients died in the hospital. Of the 25 survivors in this group who were followed up for at least 6 months, 1 patient died.

During complete A–V block, 12 patients (34 percent) manifested widened QRS complexes in escape beats (Table I). These beats had a configuration of left bundle branch block (four patients), right bundle branch block (five patients), or both (three patients).

The mean age of patients with widened QRS complexes in escape beats was 68 years and mean peak SGOT 138 IU . Two patients died of cardiogenic shock in the hospital. All 10 survivors, followed up for 6 to 17 months, are still alive. Statistically there were no significant differences in mean peak values for SGOT, immediate mortality or 6 month mortality rate between patients with widened and narrow QRS complexes in escape beats during complete A–V block (Table II).

Left Bundle Branch Block

In seven cases, escape beats with a left bundle branch block pattern were present during complete A–V block. Three of these seven patients also had left bundle branch block in conducted beats during second degree A–V block, before or after the episode of complete A–V block. Left bundle branch block in conducted beats occurred only after a critical lengthening of the R–R interval (Fig. 1). The duration of left bundle branch block ranged from 6 hours to 11 days. In six patients, left bundle branch block disappeared before 1:1 A–V conduction resumed, and in one patient (Case 5) left bundle branch block persisted for 6 days after the return to normal A–V conduction (Fig. 2).

His bundle recordings were obtained in five of the seven patients whose escape beats had a left bundle branch block configuration. In these patients, His

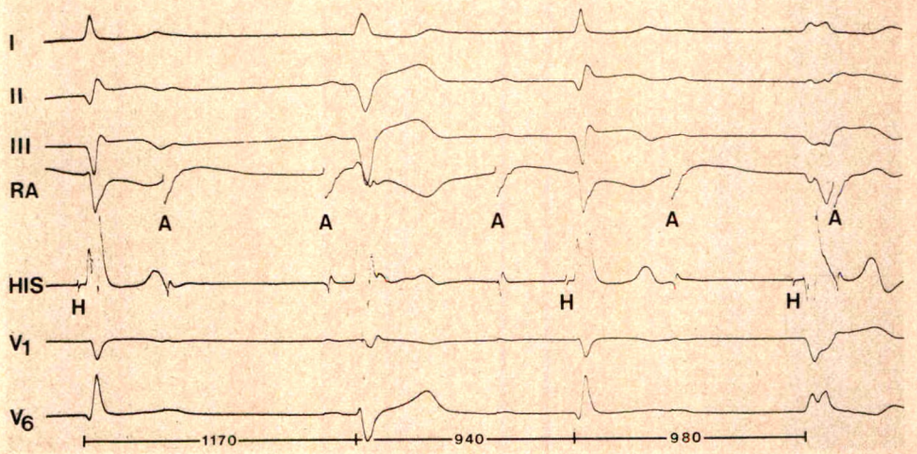

FIGURE 1. Case 4. Simultaneously recorded leads I, II, III, V_1, V_6, right atrial lead and His bundle lead. The first QRS complex is narrow and is preceded by a His bundle potential (H) at a His–V interval of 40 msec, thus indicating normal ventricular depolarization. The second QRS complex, which has a right bundle branch block configuration with left axis deviation, is not preceded by a His bundle potential, thus suggesting an origin in the inferior part of the left ventricle or near the posterior fascicle of the left bundle. The third QRS complex has all the characteristics of a nonaberrantly conducted beat. The last QRS complex shows a left bundle branch block configuration and is preceded by a His bundle potential at a His–V interval of 45 msec. As demonstrated by the intraventricular intervals, this represents a Wenckebach type of A–V conduction pattern with the development of left bundle branch block at a critical lengthening of the R–R interval. RA = right atrium.

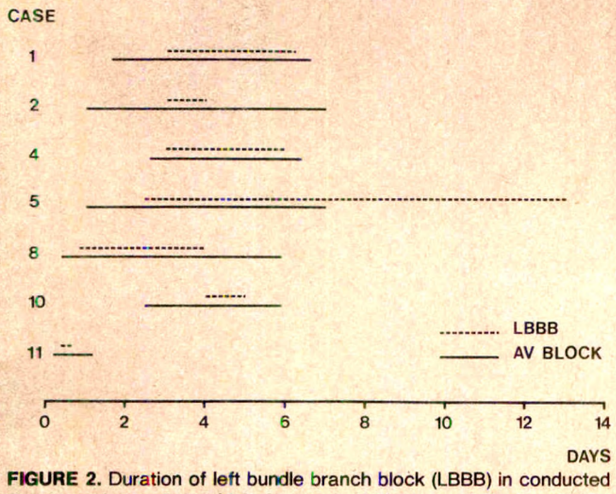

FIGURE 2. Duration of left bundle branch block (LBBB) in conducted or escape beats during high degree A–V block. In all seven patients left bundle branch block was preceded by A–V block. Left bundle branch block disappeared in six patients before 1:1 A–V conduction resumed. In one patient (Case 5) left bundle branch block persisted for 6 days after return of 1:1 A–V conduction.

bundle potentials were observed to occur 45, 45, 45, 50 and 60 msec, respectively, before the onset of the widened QRS complex. His–V intervals of escape beats with a left bundle branch block configuration were equal to those measured later in nonaberrantly conducted beats, except in one patient (Case 4) whose His–V interval was 5 msec shorter in the nonaberrantly conducted beats. In two patients pacing of the His bundle during complete A–V block revealed a bradycardia-dependent left bundle branch block (Fig. 3).

Four patients were restudied at least 6 weeks after infarction. In none of them could left bundle branch block be elicited, either at short premature beat intervals during atrial pacing or during escape beats occurring after carotid sinus massage or pacing at high rates. The functional and effective refractory period of the A–V node, as determined by the single test stimulus method during atrial pacing, was normal in three patients.

One patient (Case 1) manifested definite lengthening of the functional and effective refractory periods (600 and 510 msec, respectively, at a basic cycle length of 750 msec). At the time of restudy in the patient who previously showed a slightly prolonged His–V interval of 60 msec (Case 5) during complete A–V block in escape beats the His–V interval was still 60 msec, whereas A–V nodal conduction was normal as mentioned before. This finding suggests that temporary block within the His bundle was probably not responsible for this slightly prolonged His–V interval.

Right Bundle Branch Block

In eight patients the escape beats during complete A–V block showed a right bundle branch block configuration. The duration of appearance of these beats ranged from 4 hours to 2 days. In five of the six patients who had His bundle recordings, no His bundle activation could be recorded in or preceding the beats manifesting right bundle branch block. In one patient, the His bundle potential coincided with the beginning of the beats with a right bundle branch block configuration (Fig. 4); the latter had a QRS duration of 0.12 second and an indeterminate frontal QRS axis. In the other five patients, QRS duration ranged from 0.12 to 0.16 second, and all five patients manifested left axis deviation of the QRS complex in the frontal plane.

In all six patients with His bundle recordings, the escape beats with a right bundle branch block configuration occurred together with escape beats demonstrating narrow QRS complexes. The latter were all preceded by a His bundle potential occurring 40 to 50 msec before the QRS complex, thus indicating that the site of A–V block was located in the A–V junction. Escape beats with a right bundle branch block configuration occurred at a rate of 40 to 60/min. This

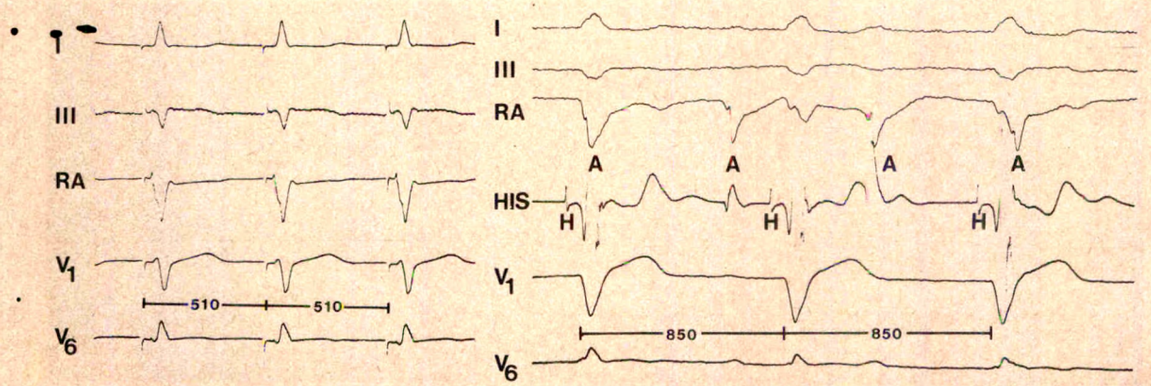

FIGURE 3. Case 5. Pacing of the His bundle revealing bradycardia-dependent left bundle branch block. **Right,** during third degree A–V block the escape beats showing a left bundle branch block configuration are preceded by a His bundle potential (H) at a His–V interval of 60 msec. **On the left,** during pacing of the His bundle, left bundle branch block disappeared at driving rates of 510 msec or less, thus indicating bradycardia-dependent left bundle branch block. Note that the interval between the stimulus artifact and onset of the QRS complex is identical to the His–V interval on the right, thus excluding the possibility that slowing of conduction in the right bundle branch was responsible for normalization of the QRS complex. RA = right atrium.

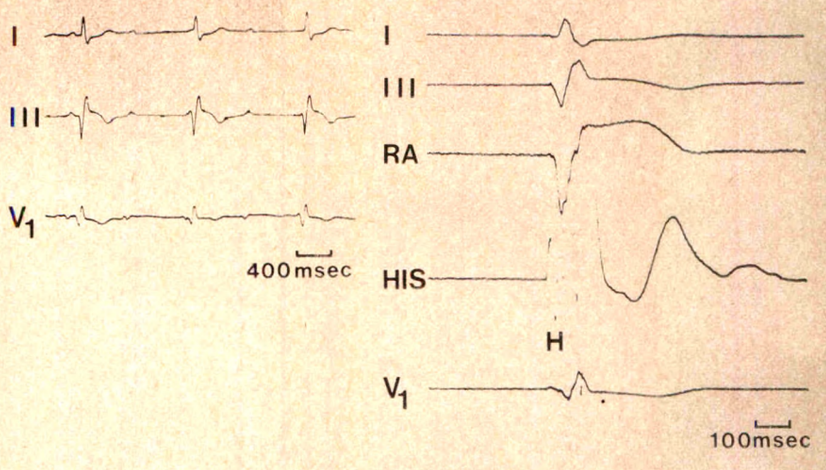

FIGURE 4. Case 1. Escape beats showing right bundle branch block configuration with an indeterminate frontal QRS axis and a QRS duration of 0.12 second during third degree A–V block **(left). On the right,** the His bundle potential (H) coincides with the onset of the escape beat with a right bundle branch block configuration, thus suggesting an origin near or in the main stem of the left bundle.

rhythm alternated with the A–V junctional escape rhythm. In three patients the frequency of the escape beats with a right bundle branch configuration was higher than that of the A–V junctional escape beats with narrow QRS complexes. In three other patients the right bundle branch block escape rhythm had a lower frequency than the A–V junctional rhythm and appeared in the presence of an unstable A–V junctional mechanism.

Discussion

Pick[19] recently listed the following six potential mechanisms for aberration of escape beats:

1. "Preferential" A–V path
2. Phase 4 depolarization
3. Ventricular (fascicular) origin
4. Functional dissociation within a bundle branch
5. Wedensky facilitation
6. Supernormality of intraventricular conduction

As he pointed out, the first and last three mechanisms are hypothetical and may apply only exceptionally.

Singer et al.[20] demonstrated diastolic phase 4 depolarization in Purkinje cells leading to aberration of late impulses. Rosenbaum et al.[21] pointed to the combination of hypopolarization and spontaneous diastolic depolarization in one of the bundle branches leading to bundle branch block. They called this phase 4 block and found coronary artery disease in most of their patients with this phenomenon.

Our electrocardiographic observations in patients with left bundle branch block are in accordance with the criteria of bradycardia-dependent bundle branch block of Massumi.[22] Sarachek[23] and Gay and Brown[24] were the first to mention the presence of bradycardia-dependent bundle branch block during high degree A–V block in inferior myocardial infarction. However, His bundle recordings are necessary to determine the site of origin of escape beats with widened QRS complexes.

A case of bradycardia-dependent bundle branch block associated with inferior myocardial infarction was described first by Bauer et al.[25] in 1965. In that case (their Patient 13) left bundle branch block occurred during sinus bradycardia. In contrast, in our group left bundle branch block occurred exclusively during high degree A–V block; before A–V block six patients manifested sinus bradycardia without left bundle branch block even at ventricular rates slower than those present during A–V block (Fig. 5). In our series of 225 patients with inferior myocardial infarction none of the 35 with sinus bradycardia (defined as a sinus rate of less than 60/min) manifested bradycardia-dependent left bundle branch block during conducted beats. We therefore assume that simultaneously occurring ischemia of the A–V junction and main stem of the left bundle was responsible for block in the A–V junction and also for phase 4 block in the left bundle branch.

We do not understand why in our patients phase 4 block always occurred in the left bundle branch. We know of no data suggesting that the slope of phase 4 depolarization is steeper in the left than in the right bundle branch.

Anatomic basis for bundle branch block in inferior infarction: Sutton and Davies,[4] reporting on 11 patients with complete heart block associated with inferior myocardial infarction, correlated the patho-

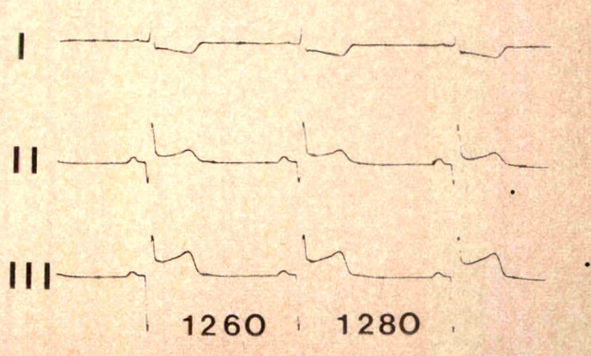

FIGURE 5. Case 4 (see Fig. 1). Electrocardiogram during sinus bradycardia with a ventricular rate lower than that in Figure 1. No left bundle branch block occurs.

logic data with the electrocardiographic findings. They found no constant relation between the presence of bundle branch block during A–V block in inferior myocardial infarction and structural damage in the bundle branches, and they considered the occurrence of bundle branch block during A–V block in inferior myocardial infarction to be related to reversible ischemia rather than to structural damage. The coincidence of left bundle branch block and high degree A–V block during the acute phase of inferior myocardial infarction suggests that a common anatomic factor is responsible for this association.

Frink and James[26] postulated two anatomic mechanisms for widened QRS complexes during A–V block in inferior myocardial infarction: (1) two vessel disease, involving both the right coronary artery and the descending branch of the left coronary artery, and (2) vascularization of the His bundle and proximal part of the bundle branches occurring exclusively through the A–V nodal artery. Since only one of our patients had a previous anterior infarction and since both left bundle branch block and A–V block were transient in the other patients, our findings seem to be more compatible with the second mechanism.

His bundle electrograms—conduction mechanisms: Our electrocardiographic observations with His bundle recordings in six patients with escape beats demonstrating a right bundle branch block configuration indicated that these beats originated below the A–V junction. In one patient (Case 1) the His bundle potential coincided with the beginning of the QRS complex with a right bundle branch block configuration, a duration of 0.12 second and an indeterminate frontal QRS axis. These findings suggest that the site of origin of this beat could be in or near the main stem of the left bundle. This type of escape beat has been described previously by Massumi and co-workers.[27]

During the electrocardiographic observations in the other five patients who had escape beats with a right bundle branch block configuration and a QRS duration of 0.12 to 0.16 second, no His bundle potential could be recorded near the beginning of the QRS complex with a right bundle branch block configuration. Since these beats demonstrated left axis deviation, their origin in the inferior part of the left ventricle or near the posterior fascicle of the left bundle seems likely. The rather high frequency (50 to 60/min) of these escape beats with a right bundle branch block configuration in six patients and the observation that in three patients the beats with a right bundle branch block pattern dominated the A–V junctional escape rhythm are suggestive of an active mechanism of impulse formation in the left ventricle. These last mechanisms are also reported in accelerated ventricular rhythms during sinus bradycardia or the slow phase of sinus arrhythmia.[28]

Our studies suggest that widening of the QRS complex of the escape pacemaker may be due either to an A–V junctional escape mechanism with phase 4 bundle branch block (which occurred in the left bundle branch in all of our patients), or to an escape rhythm located in the left ventricle, alternating with the A–V junctional pacemaker. The A–V block was situated in the A–V junction in all of our patients studied by His bundle recordings who showed widened QRS complexes in escape beats during complete A–V block in inferior myocardial infarction.

Both widening of the QRS complex and A–V block regressed within a few days. There were no significant differences in immediate mortality, 6 month mortality or mean peak values for SGOT between patients with narrow and widened QRS complexes, thus suggesting that widened QRS complexes during complete A–V block in inferior myocardial infarction have no prognostic significance.

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Platelet Survival in Patients with Prosthetic Heart Valves

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Chromium-51 platelet survival studies were carried out in 20 patients with a prosthetic heart valve. Only 1 of 10 patients with a prosthetic mitral valve had a significantly shortened platelet survival time, and the mean value of 8.3 ± 0.96 (±1 standard deviation) days was not significantly different from that of normal control subjects (8.9 ± 0.75 days). Four of 10 patients with an aortic prosthesis had a shortened platelet survival time, and the mean value of 7.8 ± 0.10 days in this group differed significantly from the normal control value ($P < 0.05$). Treatment with aspirin did not appear to alter platelet survival but, when combined with Coumadin therapy, resulted in marked prolongation of bleeding time. Our results do not support the concept that thrombus formation on the prosthesis is the cause of the shortened platelet survival time since thrombus formation is more likely to occur in mitral than aortic prostheses. Reduced platelet survival time secondary to damage by the prosthesis, similar to the problem of hemolysis in red blood cells, is a more likely explanation.

Thrombus formation on a prosthetic heart valve with subsequent embolization continues to be one of the serious complications occurring after the initial postoperative period in patients undergoing valve replacement. The frequency of this complication has differed with the valve design, with various modifications of a given valve type and also with the site of the valve, (mitral vs. aortic).[1–4] However, the trend has been toward a reduced frequency of embolic complications with the more recent valve prostheses.[1,3,5] It is thought that the process of thrombus formation on prosthetic surfaces may be primarily related to the adherence of platelets with subsequent buildup of platelet aggregates and the deposition of fibrin.[6,7] Inherent in this theory is the concept that drugs of the "antiplatelet" type might be capable of decreasing both thrombus development and subsequent embolization.[7–9] The latter has now been shown by Sullivan et al.[9,10] to be true for patients with prosthetic heart valves. Shortened platelet survival times have also been demonstrated in patients with prosthetic heart valves, as initially reported by Lander et al.[11] and confirmed by Weily and Genton[12] and Harker and Slichter[13] in larger series. Preliminary results of studies from this laboratory[14] of platelet survival in patients with prosthetic valves did not appear to agree with the observations in the latter two reports. In this report we present further data from the analysis of findings in 20 patients.

Methods

Patients: One hundred and fourteen consecutive patients with prosthetic heart valves, assigned randomly to a double-blind trial of aspirin, 300 mg daily, are being followed up at regular intervals. Twenty of these patients, selected only on the basis of living close enough to the hospital to permit daily collection of blood samples, underwent platelet survival studies. All patients were receiving sodium warfarin (Coumadin®) therapy.

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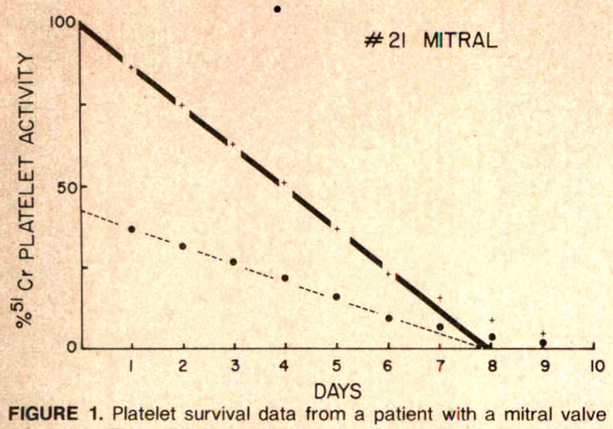

FIGURE 1. Platelet survival data from a patient with a mitral valve prosthesis. The **solid dots** represent the observed chromium-51 activity as a percent of the total ^{51}Cr platelet activity. The data from the first 6 days were used in a linear regression equation to find a theoretical 100 percent activity for day zero. The ^{51}Cr platelet activity remaining on each day was then expressed as a percent of this value (+'s). The regression line was also extrapolated to zero percent activity to find the platelet survival time in days.

Platelet survival studies: Chromium-51–labeled platelet survival studies were carried out according to the method of Aster and Jandl.[15]

Platelet aggregation: Platelet aggregation was studied by a modification of the turbidometric method described by Born,[16] using a Payton Aggregometer system (Payton Associates Limited, Scarborough, Ontario, Canada). All blood for platelet testing was collected and handled in plastic materials. Platelet-rich plasma was prepared by collecting whole blood in 3.8 percent sodium citrate, followed by centrifugation at 260 g for 10 minutes. The aggregation response to collagen and adrenalin was tested.

Platelet counts: Platelets were counted by phase contrast microscopy according to the method of Brecher and Cronkite.[17]

Prothrombin times: Quick one-stage determinations of prothrombin times were performed, using Simplastin, as described by the manufacturer (Warner-Chilcott Laboratories, Morris Plains, N. J.).

Bleeding times: Bleeding times were measured in all patients, using the modified Ivy-Template method, as described by Mielke et al.[18]

Platelet aggregation studies and determinations of prothrombin and bleeding times were performed at regular intervals in these patients; the results reported here were obtained within a month of the time of the platelet survival study.

Results

Ten of the 20 patients had received a prosthetic aortic valve and 10 a prosthetic mitral valve. Data concerning the time of the platelet survival study and type of prosthetic valves are shown in Table I.

Platelet survival studies: Figure 1 shows the platelet survival data from a patient with a prosthetic mitral valve. To remove as much bias as possible from the interpretation of data, the percent of remaining ^{51}Cr activity on each of the first 6 days was substituted into a linear regression equation and the line extrapolated to zero activity to find the platelet survival time in days. The pattern of ^{51}Cr disappearance was linear, and any tailing off over the last few days, as seen in Figure 1, involved less than 10 percent of the initial activity and a negligible population of platelets. The mean platelet survival time for six normal control subjects was 8.9 ± 0.75 (1 standard deviation [SD]) days (Table II). For the patients with a mitral valve prosthesis, the mean platelet survival time was 8.3 days, which was not statistically different from that of the normal subjects. However, the mean platelet survival time for the 10 patients with a prosthetic aortic valve was 7.8 days, which was significantly shorter than that of the normal subjects ($P < 0.05$). Analysis of the individual platelet survival times reveals that 4 of 10 patients in the aortic valve group had a platelet survival time more than 2 standard deviations shorter than the mean value of the control subjects (6.3, 6.3, 7.1 and 7.3 days, respectively), whereas only 1 of the 10 patients with a mitral valve prosthesis had a significantly shortened platelet survival time (6.9 days). The difference in frequency of shortened platelet survival times between patients in the mitral and aortic valve groups was significant ($P < 0.05$). The platelet survival times of all patients receiving aspirin did not differ significantly

TABLE I

Type of Prosthetic Valve and Time of Platelet Survival Study in 20 Patients with Mitral or Aortic Valve Replacement

	Mitral Valve Prosthesis (10 patients)	Aortic Valve Prosthesis (10 patients)
Valve type		
Starr-Edwards	5	8
Björk-Shiley	4	1
Wada	1	0
Hufnagel	0	1
Time of study (average months postoperative)	7.9	6.4

TABLE II

Chromium-51 Platelet Survival Time in Normal Control Subjects and Patients (days)

	Patient Groups	
Normal Subjects	Mitral Prosthesis	Aortic Prosthesis
8.5	8.5	7.6
8.4	9.4	7.1
8.7	7.9	8.4
8.6	7.9	8.6
10.4	8.1	7.3
8.8	10.4	6.3
...	7.8	8.6
...	8.0	6.3
...	8.2	9.2
...	6.9	8.3
8.9 ± 0.75*	8.3 ± 0.96*	7.8 ± 1.0*

* Mean ± 1 standard deviation

TABLE III

Mean Chromium-51 Platelet Survival Time (days): Effect of Treatment with Aspirin

	Patients		
	Mitral Prosthesis	Aortic Prosthesis	Total
Aspirin	8.1 (6)	7.8 (5)	8.0 (11)
Placebo	8.6 (4)	7.7 (5)	8.1 (9)

Numbers in parentheses indicate the number of patients in each group.

TABLE IV

Effect of Aspirin Treatment (means ± 1 standard deviation)

Patient Group	Platelet Survival (days)	Prothrombin Time (ratio)*	Bleeding Time (min)	Platelet Aggregation (no. inhibited)
Aortic prothesis	7.8 ± 1.0	16.7 ± 0.32	...	...
Mitral prosthesis	8.3 ± 0.96	16.7 ± 0.30	...	...
Aspirin	8.0 ± 0.74	16.7 ± 0.34	16.7 ± 9.4	11/11
Placebo	8.1 ± 1.3	16.7 ± 0.28	8.3 ± 3.0	1/9

* Prothrombin time ratio = patients' prothrombin time in seconds divided by the control time.

from the values for all patients receiving placebo. Similarly, no differences due to aspirin treatment were noted within the mitral valve group alone or the aortic valve group alone (Table III).

The size of the prosthesis did not correlate with platelet survival time. Of the four patients in the aortic valve group with a shortened platelet survival time, two had Starr-Edwards no. 9, and two had a Starr-Edwards no. 10 valve. The remaining six Starr-Edwards aortic valves were also size 9 or 10, except for one no. 8. The platelet survival time was 9.2 days in the patient with the latter valve.

Platelet counts: At the time of the platelet survival study, 18 of the 20 patients had a platelet count of 188,000 to 400,000/mm^3 (mean 241,000; normal range 150,000 to 400,000/mm^3). Platelet counts performed at 3 month follow-up visits, both before and after the platelet survival study, tended to be quite constant for any individual patient with a maximal range of 100,000 and no tendency to either rise or fall with time. Two of the 20 patients had slightly decreased platelet counts of 129,000/mm^3 and 125,000/mm^3, respectively, with platelet survival times of 7.9 and 7.3 days. Their platelet counts before and after the survival time did not vary by more than 10,000/mm^3. Of the five patients with short platelet survival times, one had a low count (125,000/mm^3) and the others a normal count (180,000, 240,000, 310,000 and 340,000/mm^3).

Prothrombin times: To produce a single figure for analysis, each patient's prothrombin time was divided by the control time and expressed as a ratio (Table IV). No significant differences were noted between patients with mitral and aortic valve prostheses or between those treated by aspirin and placebo. The "prothrombin time ratios" for the five patients with a shortened survival time were 1.3, 1.6, 1.4, 1.2 and 1.4, respectively (mean 1.4). This mean value differed statistically from the mean of the remaining patients (1.8; $P < 0.01$).

Bleeding times: Patients receiving aspirin had a significantly longer bleeding time than those receiving placebo ($P < 0.05$; Table IV).

Platelet aggregation: Aggregation results are reported as the number of patients demonstrating the inhibiting effect of aspirin, as evidenced by the lack of a second phase in response to adrenaline and a significantly diminished response to collagen. With the exception of one patient in the placebo group whose platelet aggregation was inhibited, the patients' aggregation curves were as expected, inhibited in the aspirin group and normal in the placebo group.

Discussion

Lander et al.[11] demonstrated slightly shortened platelet survival times in two of five patients with a prosthetic mitral valve and in one of two patients with a prosthetic aortic valve. Weily and Genton[12] reported reduced platelet survival times in 15 of 16 patients with a prosthetic mitral valve. The shortening to a mean of 5.49 days was significant when compared with 6.73 days for normal control subjects ($P < 0.001$). Harker and Slichter[13] demonstrated marked shortening in patients with mitral (5.2 days) and aortic (6.5 days) valve prostheses compared with findings in normal subjects (9.5 days). The small difference between the two patient groups was significant. In our study, the platelet survival time was within normal limits in 9 of 10 patients with a prosthetic mitral valve and 6 of 10 with a prosthetic aortic valve. The mean platelet survival time for patients with a mitral valve prosthesis of 8.3 days was not significantly different from that of normal subjects (8.9 days), but that for patients in the aortic valve group (7.8 days) was significantly shortened. These results differ from the findings previously cited in that the shortening of platelet survival time was generally less frequent and less marked. In addition, the shortening appeared to be more a feature of aortic than of mitral valve prostheses.

No correlation between bleeding and platelet survival times could be demonstrated despite the markedly prolonged bleeding time in the aspirin-treated patients (Table IV). The prolongation of the bleeding time was greater than one would expect from administration of aspirin only in a dose of 300 mg daily.[18] Similarly, Coumadin alone in doses sufficient to achieve a therapeutic level of anticoagulation does not significantly prolong bleeding time,[19] and our patients receiving Coumadin alone had a normal bleed-

ing time (placebo group, Table IV). These results, which suggest that the observed prolongation of bleeding time is a result of a combined effect of aspirin and Coumadin on the hemostatic mechanism, are in agreement with the findings of O'Reilly et al.[19] The platelet counts in our patients were in the normal range except for a slight reduction in two patients (125,000 and 129,000/mm^3) and, as in the study by Harker and Slichter,[13] there was no correlation with the platelet survival time.

Platelet aggregation studies (Table IV) confirmed that aspirin-treated patients were obtaining the desired inhibitory effect on "in vitro" platelet tests. The studies also provided evidence of drug compliance in both the aspirin- and placebo-treated groups. This "in vitro" evidence, together with the prolonged bleeding time as "in vivo" evidence, does suggest that platelet function was being inhibited by treatment with aspirin. No effect of aspirin on platelet survival was demonstrated although the degree of shortening was so small that any beneficial drug effect would be difficult to observe.

The prothrombin time results appear to bear some relation to platelet survival time. The mean prothrombin time for the five patients with a shortened platelet survival time was significantly different from that of the remaining patients. However, the mean for all patients in the aortic and mitral valve groups differed with respect to platelet survival time but did not differ with respect to prothrombin time. Harker and Slichter[13] did not observe any effect of prothrombin time on platelet survival.

No relation was noted between the size of the prosthetic valve and platelet survival time. Harker and Slichter[13] did find a correlation between the nonendothelialized surface area and platelet destruction.

Relation to clinical thromboembolic episodes: Harker and Slichter[13] concluded that platelets may undergo destruction through thrombus formation on prosthetic valves and that the best indicator of this occurrence is a shortened platelet survival time. Their hypothesis would explain the greater degree of shortening in patients in the mitral valve group since they have a greater frequency of thromboembolic complications. Weily and Genton[12] concluded that platelet abnormalities regularly occur in patients with a mitral valve prosthesis and that these abnormalities may contribute to thromboembolism. They considered platelet survival time a more sensitive measure of altered platelet kinetics than platelet adhesiveness or aggregation. The rate of occurrence of embolic complications in our study was similar to that of other reports. Three definite episodes have been reported in 58 patients with a prosthetic aortic valve (5 percent) and five episodes in 35 patients with a mitral valve prosthesis (14 percent). On the other hand, platelet survival times were normal in all but 1 of the 10 patients in our mitral valve group but were shortened in 4 of the 10 in our aortic valve group. This observation casts some doubt on the hypothesis that shortened platelet survival is related to the development of thrombotic material on a valve and subsequent embolization.

A possible explanation for the difference observed in the prevalence and severity of shortened platelet survival in our study may lie in the valve design. Eight of the 10 aortic valves, and 5 of the 10 mitral valves were of the Starr-Edwards type, and all were of the more recent cloth-covered design. Embolic complications are less frequent with these newer valves.[1,3,5] Thus, if the assumption is correct that a decreased tendency to thrombus formation and subsequent embolization will be associated with normal platelet survival time, then a higher percentage of patients with a normal platelet survival time would be expected with the more recent valve designs. Weily et al.[20] recently reported normal platelet survival time in six of nine patients with a Beall mitral valve prosthesis.

Aortic vs. mitral valve prosthesis: The explanation just given would not account for the greater prevalence and severity of the shortened platelet survival times in the patients with an aortic rather than a mitral valve prosthesis. An alternative hypothesis is that platelets undergo more damage in passing over the aortic valve region where the flow rates and pressures are considerably greater than they are in the region of the mitral valve. This increased damage may be comparable to the increased frequency of significant hemolysis in association with aortic valve prostheses.

Acknowledgment

The skilled technical assistance of B. S. Mann, M. Gulka, D. A. Nelson and D. J. Barker is gratefully acknowledged.

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Encephalogenic Cardiomyopathy After Stimulation of the Brain Stem in Monkeys

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Repeated electrical stimulation of the brain stem including the hypothalamus, pons and medulla in monkeys produced an increase in arterial blood pressure, cardiac arrhythmias, various degrees of S–T segment or T wave changes and structural damage to the myocardium. The following ultrastructural changes in the myocardium occurred: distension of sarcoplasmic reticulum, swelling of mitochondria, disarrangement of filamentous arrays, formation of contraction bands, dissociation of intercalated discs and focal necrosis. These changes are similar to those found in ischemic myocardial tissue and myocardial necrosis induced by catecholamines. The myocardial lesions are probably related to activation of the sympathetic mechanism in the brain stem.

Electrocardiographic changes simulating myocardial ischemia have been well documented in patients with cerebrovascular accidents, head injury and other intracranial disorders.[1–7] However, positive findings of myocardial lesions have not been consistently reported at autopsy.[1,3,4,6,7] Comparatively few experimental investigations have been performed to correlate electrocardiographic changes induced by irritation of the central nervous system with possible myocardial lesions. Porter et al.[8] observed no histologic evidence of myocardial damage in cats after stimulation of the hippocampus and amygdala, in spite of sustained electrocardiographic abnormalities. Burch et al.[9] produced myocardial lesions in mice by injection of blood into the cranium, but electrocardiography was not performed. Eichbaum et al.[10,11] studied electrocardiographic changes in dogs and guinea pigs after head trauma or an increase in intracranial pressure, but did not examine the myocardium microscopically. Melville et al.[12] succeeded in producing myocardial damage in some but not all cats displaying cardiac arrhythmias and ST–T changes after prolonged electrical stimulation of the pressor areas of the hypothalamus. Greenhoot and Reichenbach[13] have reported a high frequency of myocardial damage and electrocardiographic abnormalities both in patients with subarachnoid hemorrhage and in cats after electrical stimulation of the midbrain pressor areas.

In this investigation in monkeys we attempted to study the electrocardiographic changes and the fine structural alterations of the myocardium after electrical stimulation of the brain stem, and to determine which specific sites, when stimulated, are associated with cardiac damage.

Methods

Recording of electrocardiogram and blood pressure: Ten monkeys (Macaca cyclopis) of either sex, weighing 5 to 7 kg, were lightly anesthetized with sodium pentobarbital, 25 to 30 mg/kg injected intraperitoneally. The trachea was intubated to assure free ventilation. The femoral artery was cannulated and the arterial blood pressure monitored with a Statham P23AC

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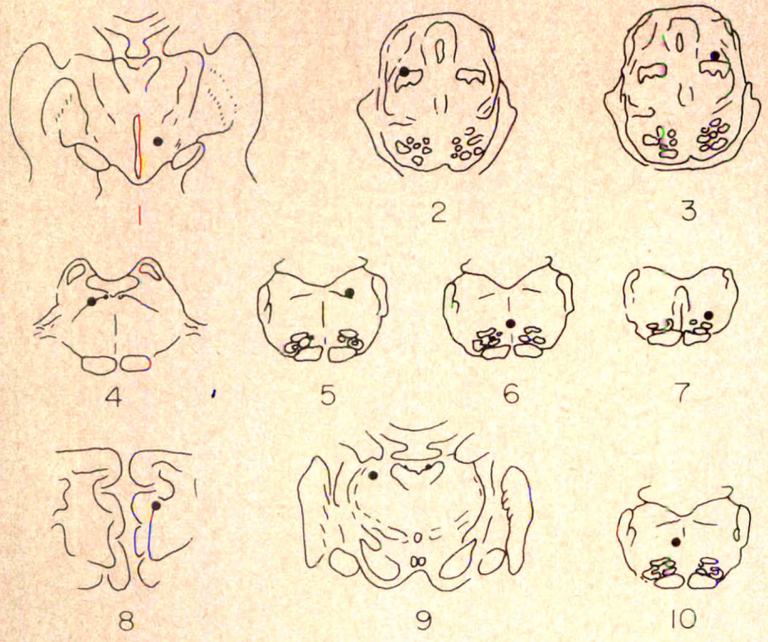
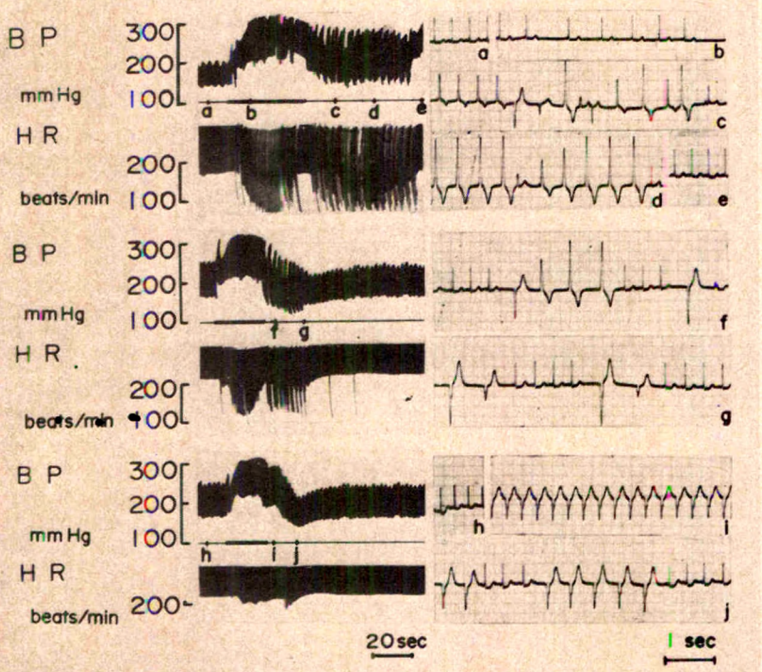


FIGURE 1. Stimulation sites of the brain in the 10 experimental and control monkeys.



Signal marks (a-j):

1st stimulation (Top)
a - before stimulation
b - during stimulation
c, d, e - 15, 35 and 58 sec after stimulation

5th stimulation (Middle)
f, g - 5 and 20 sec after stimulation

46th (Last) stimulation (Bottom)
h - before stimulation
i, j - 3 and 15 sec after stimulation

FIGURE 2. Monkey 3. Changes in blood pressure (BP), heart rate (HR) and electrocardiogram induced by stimulation of the tegmentum of the lower pons. Stimulations (**heavy bars** between blood pressure and heart rate tracings) were repeated 46 times at intervals of 10 to 15 minutes. The electrocardiogram, taken at the time as marked on the signals (a to j) of the slow speed tracings, is shown in the **right panels. Top tracing** depicts the changes induced by the first stimulation. Note the increased blood pressure (102 mm Hg) and sinus bradycardia during stimulation (b), and the poststimulatory cardiac arrhythmias (nodal rhythm, bidirectional and multifocal ventricular ectopic beats) (c, d). The arrhythmias persisted for 55 seconds. Note also the slight S–T depression after the rhythm had converted to normal (e). **Middle tracing** depicts changes induced by the fifth stimulation. Note the similar arrhythmias and the more marked S–T depression (f, g). **Bottom tracing** shows changes induced by the final (46th) stimulation. Note the poststimulatory ventricular tachycardia (i) and the prominent S–T depression (j).

transducer. Heart rate was monitored with a Grass 5P4 tachometer which was triggered by the arterial pulses. These recordings were made on a Grass 5D polygraph. The electrocardiogram was monitored with a Hewlett Packard 1500A recorder.

Application of electrical stimulation: The head of the animal was fixed in a David-Kopf stereotaxic instrument, and the desired areas of the brain were located and stimulated with a unipolar electrode (outer diameter 0.6 mm). Stimulation was provided by a Grass S4 rectangular pulse generator coupled with an isolation unit. The parameters for stimulation were 50 Hz, 2 msec and 5 to 12 v. Each stimulation lasted 15 to 35 seconds. The stimulation was repeated 5 to 10 minutes after the electrocardiogram demonstrated reversion to sinus rhythm. In each experiment, except for one in which a single stimulation produced cardiac arrhythmias lasting 57 minutes, the stimulations were repeated 15 to 46 times. Stimulations were repeated until the total duration of cardiac arrhythmias had reached 25 minutes or more, or until the electrocardiogram had shown a definite change in the S–T segment or T wave, or both.

Examination of the myocardium: At the end of the experiment, the chest was opened and the heart removed from the anesthetized animal. Myocardial tissue was taken immediately from the left ventricular wall and interventricular septum. For light microscopy, the tissue was fixed in 10 percent formalin, embedded in paraffin, sectioned and stained with hematoxylin-eosin. A conventional histochemical technique for succinic dehydrogenase activity was performed using frozen sections.[14] Preparation for electron microscopy consisted of double fixation in 3 percent buffered glutaraldehyde and 1 percent osmium tetroxide with Millonig's buffer, and embedding in epon 812.[15] Sections were cut on a Porter Blum MT-1 ultramicrotome, double-stained with uranyl acetate and lead citrate, and examined with a Hitachi HU-11E microscope.

TABLE I

Electrocardiographic Changes in 10 Monkeys After Electrical Stimulation of the Brain

Monkey no.	Stimulation: Site	Stimulation: Times of Repetition	Elevation of Blood Pressure (mm Hg)	Electrocardiographic Changes	Sum Duration of Cardiac Arrhythmias (min)
1	Posterior hypothalamus	38	47	Sinus tachycardia, bigeminal VPCs, VT, marked S–T depression	21
2	Left tegmentum of lower pons	40	56	Bigeminal VPCs, nodal rhythm, slight S–T elevation, increased T wave amplitude	25
3	Right tegmentum of lower pons	46	102	Sinus bradycardia, nodal rhythm, bidirectional & multifocal VPCs, VT, marked S–T depression	28
4	Left dorsolateral upper medulla	1	46	Sinus bradycardia with atrioventricular block, bigeminal & multifocal VPCs, VT, marked S–T elevation	57
5	Right dorsolateral mid-medulla	15	54	Sinus bradycardia (initial), sinus tachycardia (late), slightly increased T wave amplitude	—
6	Midline of ventral lower medulla	39	44	Nodal rhythm, intermittent & multifocal VPCs, supraventricular tachycardia, increased T wave amplitude	24
7	Right ventrolateral lower medulla	21	59	Slight sinus tachycardia, slight S–T depression	—
8	Parietal lobe	40	—	No remarkable changes	—
9	Thalamus	38	—	No remarkable changes	—
10	Midline of mid-medulla	35	66	No remarkable changes	—

VPCs = ventricular premature contractions; VT = ventricular tachycardia.

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Localization of stimulation sites of the brain: The brain was perfused with normal saline solution followed by 10 percent formalin in saline solution, and then fixed in 10 percent formalin for several days. Brain sections, 40 μ in thickness, were cut using a cryostat and then stained with Weil's method. The sites of electrical stimulation were traced from the electrode tract and diagrammed as shown in Figure 1. They were distributed as follows: posterior hypothalamus (Monkey 1), tegmentum of lower pons (Monkeys 2 and 3), dorsolateral reticular formation of upper medulla (Monkey 4), dorsolateral portion of mid-medulla (Monkey 5), ventral portion of lower medulla (Monkeys 6 and 7), parietal lobe (Monkey 8), thalamus (Monkey 9) and mid-medulla (Monkey 10).

Results

Changes in electrocardiogram and blood pressure: Table I summarizes the changes in the electrocardiogram and blood pressure in the 10 animals after stimulation of the brain. Stimulation of the parietal lobe and the thalamus in the two control animals (Monkeys 8 and 9) produced no significant changes. Stimulation of the brain stem including the hypothalamus, pons and medulla consistently evoked an increase in blood pressure ranging from 44 to 102 mm Hg. Electrocardiographic changes simulating myocardial ischemia (elevation of S–T segment or increased amplitude of the T wave, or both) were observed in all but one animal (Monkey 10). The changes usually occurred after the first stimulation. They were mild and transient at first, but became progressively more prominent and persistent upon repeated stimulations. Monkeys 5 and 7 manifested only slight sinus tachycardia or bradycardia, or both. Other animals displayed profound cardiac arrhythmias including nodal rhythm, various forms of ventricular premature contractions and ventricular tachycardia. Figure 2 shows a typical example of these changes. The ectopic beats usually persisted for 10 to 55 seconds and then returned to sinus rhythm unless repeated stimulation was given. In one excep-

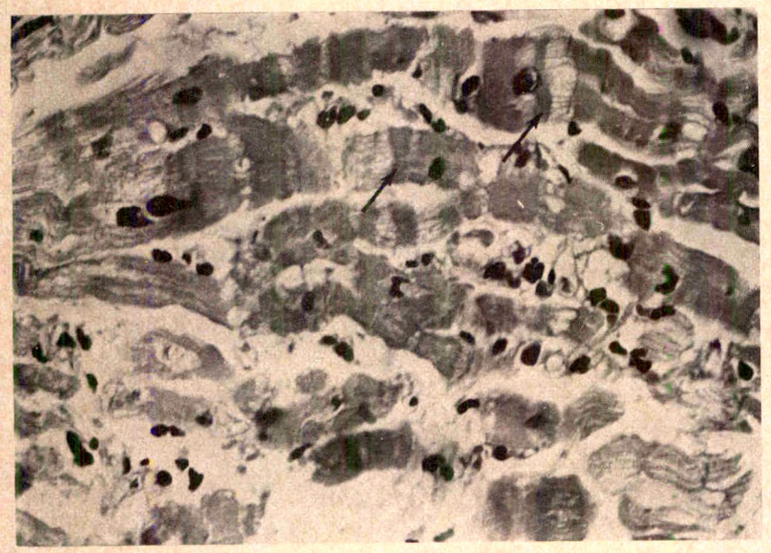

FIGURE 3. Monkey 4. Section of myocardium. Note the contraction bands of myofibers **(arrows)** associated with necrosis of individual muscle fibers. (Hematoxylin-eosin ×600, reduced by 32 percent.)

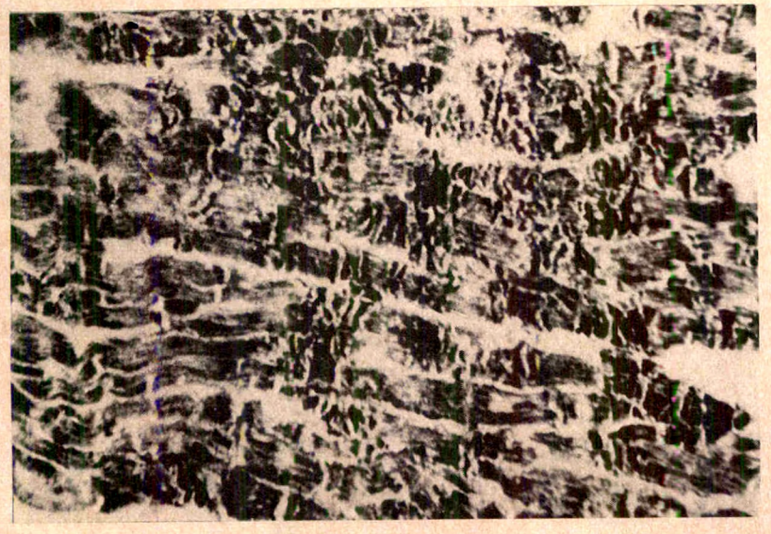

FIGURE 4. Monkey 3. Histochemical preparation of succinic dehydrogenase in the myocardium. Note the zonal distribution of the enzymatic overactivity. (Nitro blue tetrazolium ×400, reduced by 36 percent.)

tional animal (Monkey 4), a single stimulation triggered ventricular extrasystoles for 57 minutes.

Light microscopic findings: The seven animals (Monkeys 1 to 7) displaying S–T segment or T wave changes, or both, upon electrical stimulation of the brain stem all showed scattered and isolated patches of myocardial damage in the ventricular wall and interventricular septum without noticeable gross changes. The severity of the myocardial lesions ranged from hyalinization of muscle fibers to complete myocytolysis and, more frequently, foci of necrotic myocytes with widened interstitial spaces containing fibroblasts and macrophages at the subendocardial region (Fig. 3). In some areas the myofibers were overcontracted and exhibited coarse, coalescent transverse or oblique bands or more intense eosinophilic-stained material (Fig. 3). Degenerative changes were not found in the three monkeys (Monkeys 8 to 10) that had no significant electrocardiographic changes.

Histochemical findings: The myocardium of the seven monkeys with electrocardiographic changes and myocardial damage demonstrated by light microscopy all showed an uneven pattern of succinic dehydrogenase activity (Fig. 4). This was characterized by areas of increased enzymatic activity at the borders of the clear zones, which represent the intercalated discs. The distance between the discs was markedly shortened. In the other three monkeys with no abnormal electrocardiographic findings, the succinic dehydrogenase activity in the myocardium was homogeneously and evenly distributed.

Electron microscopic findings: The two control animals (Monkeys 8 and 9) stimulated at the parietal lobe and the thalamus had a normal electrocardiogram and normal appearance of the fine structures of the myocardium. The appearance conformed in general to previous descriptions of normal mammalian myocardium.[16,17] The myofibers were moderately contracted with regular periodic bands. Mitochon-

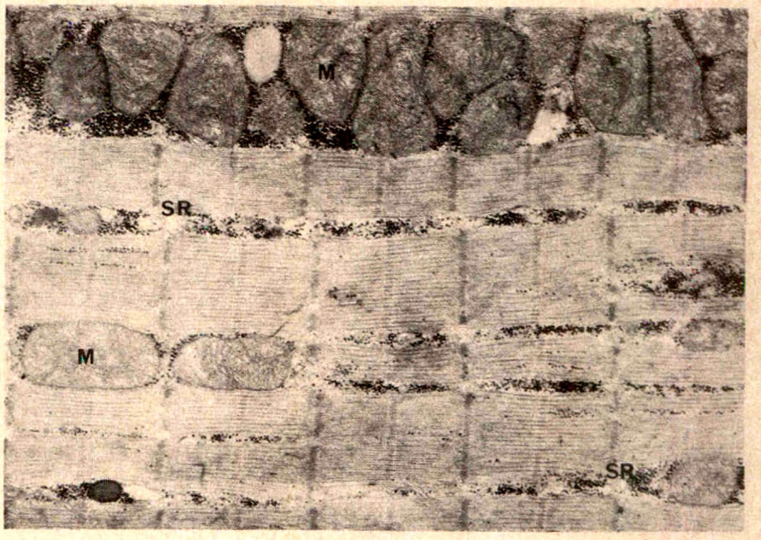

FIGURE 5. Monkey 8. Electron microscopic section of myocardium. Note the moderately contracted myofibrils, the normal mitochondria (M) and sarcoplasmic reticulum (SR). (×22,500, reduced by 36 percent.)

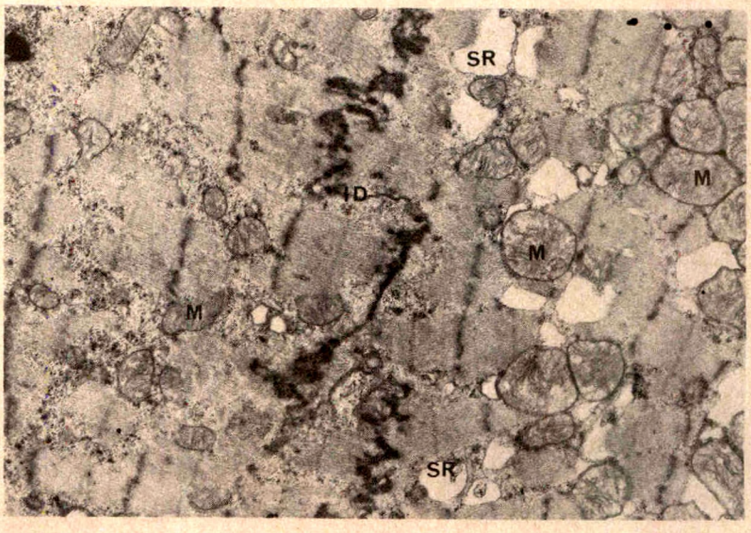

FIGURE 6. Monkey 1. Myocardium showing portions of two myofibers as demarcated by an unduly marked intercalated disc (ID). Note that the myofiber on one side contains swollen mitochondria (M), distended sarcoplasmic reticulum (SR) and tubular system. Glycogen granules are scant. On the other side, the mitochondria are scarce and shrunken and glycogen particles abundant. (×13,250, reduced by 36 percent.)

dria were normal, and glycogen particles and occasional lipid droplets were present among the myofibrils (Fig. 5).

In animals displaying slight electrocardiographic changes after stimulation at the dorsolateral mid-medulla (Monkey 5), ventrolateral lower medulla (Monkey 7) and midline area of mid-medulla (Monkey 10), there were mild degenerative changes with preservation of the intracellular organelle relations. Only the sarcoplasmic reticulum and transverse tubular system occasionally appeared prominent and dilated.

The five animals (Monkeys 1 to 4 and 6) that manifested cardiac arrhythmias associated with ST–T changes upon stimulation of the brain stem had severe ultrastructural abnormalities of the myocardium. Degenerative and necrotic changes of myofibers were readily demonstrated in many tissue blocks, especially those from the subendocardial region. These changes closely simulated those induced by injection of sympathomimetic amines[18–22] and those observed in the early stage of myocardial ischemia.[16,23] A number of myofibers showed distended sarcoplasmic reticulum and swollen mitochondria. In some sections two neighboring myofibers demarcated by an intercalated disc displayed different degrees of damage (Fig. 6). The intercalated discs showed an increased electron density. The structure of sarcomeres were indistinct. In longitudinal sections typical dense contraction bands were present throughout (Fig. 7). At each end of the contraction bands the relatively intact sarcomeres were overstretched and the intercalated disc at one end was torn apart (Fig. 7). Mitochondria were trapped in the contraction bands and were degenerating. In the more advanced instances, many foci of necrosis were observed within the myocytes. The necrosis was unrelated to the intercalated discs and often extended across the latter. In the necrotic myocytes there were broken and fused myofibrils and degenerated and disorganized mitochondria

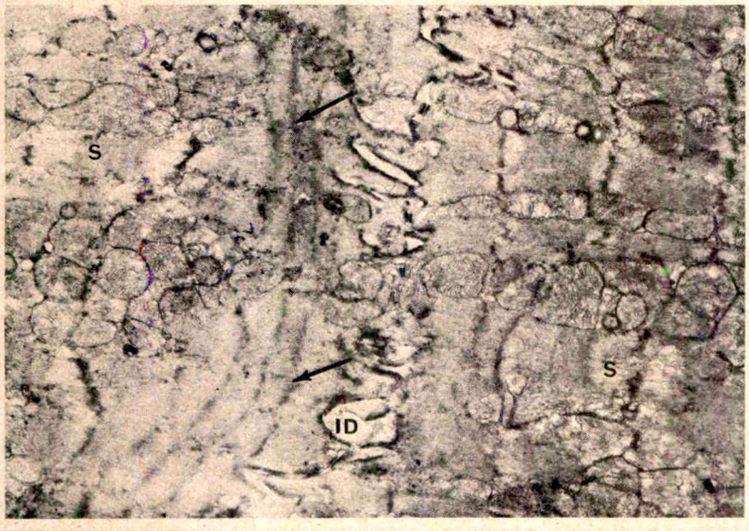

FIGURE 7. Monkey 4. Myocardium showing contraction bands of actin and myosin filaments **(arrows)** in damaged myofibers. Note also the overstretched sarcomeres (S) and separated intercalated disc (ID) at both sides of the contraction bands. (×13,250, reduced by 36 percent.)

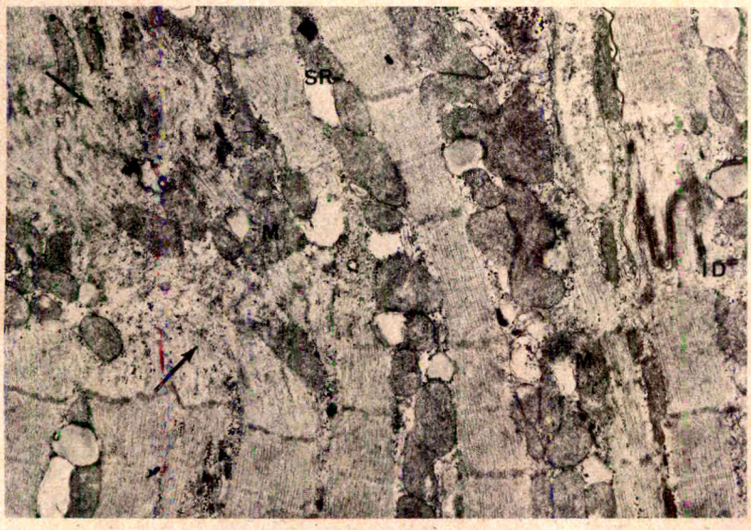

FIGURE 8. Monkey 6. Myocardium showing focal myocytolysis. Note destruction of sarcomeres **(arrows)**, degeneration of mitochondria (M) and distension of sarcoplasmic reticulum (SR). (×13,250, reduced by 36 percent.)

associated with fat droplets (Fig. 8). The nuclei showed margination and clumping of chromatin granules along nuclear membrane with rarefied nucleoplasm.

Discussion

Mechanism of myocardial damage after brain stem stimulation: Our investigation shows that stimulation of the brain stem in monkeys can produce myocardial damage in association with hypertension, cardiac arrhythmias and ST–T abnormalities. We found that stimulation not only of the hypothalamus[12,24] and midbrain,[13] but also of the pons and medulla, can produce these changes. The development of myocardial damage depended greatly on which site in the brain was stimulated. A single electrical stimulation of the dorsolateral reticular formation of the upper medulla (Monkey 4) elicited marked vasomotor reactions, prolonged cardiac arrhythmias, profound S–T segment elevation and considerable structural damage to the myocardial fibers, as demonstrated by both light and electron microscopy. Stimulation of the hypothalamus, pons and other areas of the medulla produced similar changes in the electrocardiogram and blood pressure and similar myocardial damage. Repeated stimulation of the thalamus and the parietal lobe evoked no significant cardiovascular or myocardial changes. Because the thalamus and parietal lobe have little autonomic function, this observation suggests that the autonomic nervous system is involved in the production of myocardial lesions. Increased sympathetic discharge after stimulation of the brain stem may release norepinephrine from the nerve ending in the heart and result in the production of myocardial damage. Similar changes have been produced after stimulation of the stellate ganglia[25] or parenteral injection of sympathomimetic amines such as epinephrine, norepinephrine and isoproterenol.[18–22] In these studies, focal myocardial lesions were produced which were similar to those found in our experiment. In patients with various intracranial disorders[1,4,6,7] and in experimental intracranial hemorrhage,[9] myocardial lesions were not always found, possibly because the appropriate areas of the brain were not consistently involved or stimulated. In addition, the early myocardial lesions produced by coronary occlusion[16] and injection of sympathomimetic agents[18,20,21] are reversible in nature[23,26] and, in patients who die of intracranial disease, sometimes are completely abolished before death.

Our findings suggest that physiologic and structural changes of the myocardium are both relevant to early ischemia. The mitochondrial abnormalities shown histochemically are characteristic of early ischemic or hypoxic injury,[9,27,28] as are the fine structural changes of mitochondria and sarcoplasmic reticulum. Coronary arterial constriction[24] and increased myocardial oxygen requirement[29] by local release of norepinephrine could mediate the myocardial ischemic lesions associated with ST–T segment alterations we observed in the experimental animals. The strongly contracted myofibrils seen occasionally in myocytes may indicate an immediate effect of catecholamines on the contractile elements since similar abnormalities have been produced in animals 6 to 10 minutes after injection of isoproterenol.[18]

Role of cardiac arrhythmias: In our studies, myocardial damage was more severe in monkeys that had marked cardiac arrhythmias. We believe that cardiac arrhythmias may contribute to myocardial damage by reducing the efficiency of cardiac function and impairing blood supply to the myocardium. However, two animals that had ST–T alterations with only slight changes in sinus rate and no ectopic beats had fine structural lesions in the myocardium. This finding is in agreement with the observations of Melville et al.[24] and indicates that this type of myocardial damage can occur in the absence of arrhythmias.

Other neurohumeral mechanisms: Other mechanisms of myocardial damage in these experiments seem unlikely. Anesthesia and experimental preparations in the control animals that underwent stimulation of the thalamus and parietal lobe were not accompanied by physiologic or morphologic cardiac changes. Also, there was little to suggest morphologically that the damage was related to adrenal cortical secretion or electrolyte disturbance. Corticosteroids and phosphate can produce striking mitochondrial changes with calcium deposition in the matrix,[30] but we did not observe these alterations. Myocardial damage can also be produced after stimulation of the midbrain in animals that have undergone adrenalectomy.[13] Potassium deficiency produces slackened myofibrils, severe cellular edema and sometimes myofibrilar destruction and necrosis.[31] These findings were not quite similar to those observed in our experiments. Patients with stroke or head injury who manifested electrocardiographic changes suggesting myocardial ischemia did not have electrolyte imbalance.[6,7] However, further studies will be required to elucidate the ultimate neurohumoral mechanism involved in the pathogenesis of encephalogenic cardiomyopathy.

Acknowledgment

We thank Drs. C. T. Loo and T. M. P'eng for their support and encouragement throughout the course of this investigation. We are also grateful to Mr. N. C. Chang for technical assistance.

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Reflex Inhibitory Effects of Vagal Afferents in Experimental Myocardial Infarction

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In experimental myocardial infarction with hypotension, low output state and shock (produced by injection of 0.2 ml of metallic mercury into the circumflex coronary artery of closed chest anesthetized dogs) serial recordings were made of postganglionic sympathetic and aortic baroreceptor nerve activity in addition to cardiac output, mean blood pressure, electrocardiogram and heart rate. With the decrease in cardiac output and mean blood pressure after injection of mercury, aortic nerve activity decreased as expected but, contrary to expectations, postganglionic sympathetic nerve activity also decreased. It was postulated that this decrease was due to a powerful cardiac vagal afferent reflex that could override the compensatory increase of sympathetic activity usually present with systemic baroreceptor withdrawal. Cutting or blocking the vagus nerves resulted in an immediate increase in sympathetic nerve activity followed by increases in cardiac output, mean systemic blood pressure and aortic nerve activity. Atropine, although it increased heart rate, did not reproduce the effect of vagotomy on sympathetic activity and cardiac output.

Recent renewed interest in the role of vagal afferents originating in the heart, primarily in the left ventricle and left atrium, has stimulated a number of investigators to study the reflex functions of the cardiac baroreceptors in myocardial infarction and cardiogenic shock. Several studies[1–7] have shown that in experimental coronary artery occlusion and myocardial infarction vagally mediated depressor reflexes may be present and increased activity from vagal afferent nerves originating in the left ventricle can be demonstrated. Other studies[8–12] have not confirmed the existence of depressor reflexes originating in the left ventricle during experimental coronary occlusion.

The problem has clinical importance because marked bradycardia and hypotension are common complications of myocardial infarction in man, particularly in the early phase. Some investigators[13,14] have suggested that the low cardiac output in patients with such complications is due, in addition to impaired cardiac pump function, to inadequate venous return.[13,14] However, many patients may also have a lack of adequate compensatory increase in systemic flow resistance despite the decreased cardiac output and hypotension,[15,16] thus indicating a depressor mechanism that may be partially responsible for the decreased cardiac output, inadequate distribution of blood flow and change in compensatory resistance.

The somewhat conflicting results in experimental myocardial infarction are perhaps due to different techniques used in producing coronary artery occlusion or myocardial infarction, or both, and to the different types of preparations used to study the reflex. It is well known that thoracotomy in open chest preparations used in many of the reported studies results in an increase in heart size that may tend to decrease the responsiveness of left ventricular baroreceptors. Sub-

From the Cox Heart Institute, Dayton, Ohio. This work was supported by U. S. Public Health Service Grant HL-09885 and Grant LH-15004 of the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. Manuscript accepted October 17, 1973.

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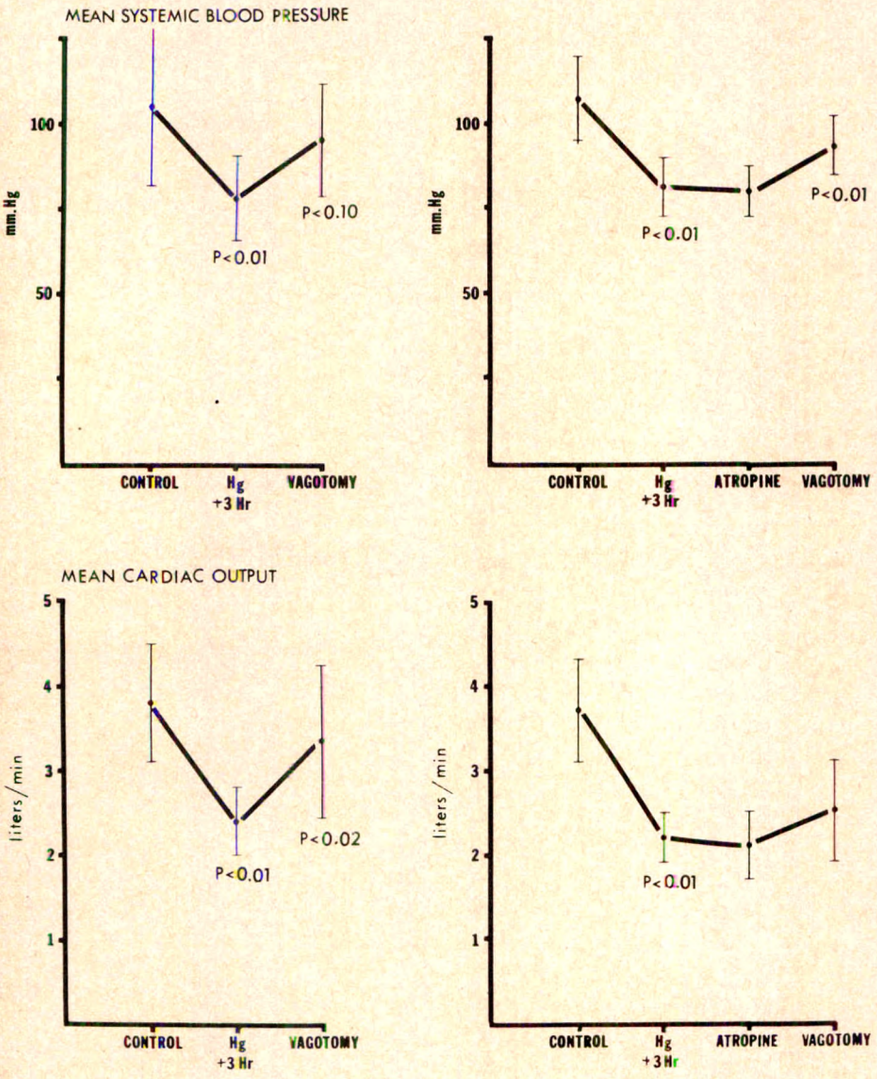

FIGURE 1. Changes in mean blood pressure and cardiac output after 3 hours of hypotension and shock and subsequent disruption of vagal trunks in seven dogs **(left graphs)** and response to atropine (0.1 mg/kg) in five animals with shock. Thirty minutes after atropine vagal trunks were severed **(right graphs).** Horizontal bars are standard deviations of means. *P* values indicate significance of differences between previous state and the state below which the *P* value is shown. Where no value is shown the difference was not significant.

sequent experimental coronary occlusion may not result in the same reflex effects as occlusion in a closed chest preparation. In addition, opening of the pericardium may also change ventricular receptor response, and isolation of the anterior descending coronary artery for placing an occluding cuff may destroy afferent nerve fibers originating in the ventricle. Frink and James[17] have shown that the fibers mediating the vagal reflex are located beside the anterior descending and main left coronary arteries in the dog.

To eliminate some of these objections with the open chest preparation, we decided to restudy this problem in the closed chest animal using a previously described technique of selective coronary artery catheterization and production of myocardial infarction with cardiogenic shock.[18] We have previously reported our studies of the hemodynamic changes resulting from the extensive myocardial infarction and shock using this technique in 68 closed chest animals.[19,20] In this report we present our studies on the effect of vagal afferents on heart rate, cardiac output, mean systemic blood pressure and renal postganglionic sympathetic discharge during the development of decreased cardiac output and hypotension using our closed chest technique of experimental myocardial infarction. Atropine was given to evaluate its effectiveness in blocking this vagal inhibitory reflex. The reflex was subsequently interrupted by cutting both vagal trunks while leaving the systemic baroreceptors (aortic and carotid sinus) intact. Our results indicate that vagal afferents, especially those originating in the left ventricle, probably play a role in the prolonged depression of cardiac output, mean systemic blood pressure and sympathetic activity in cardiogenic shock.

Method

Twelve mongrel dogs of both sexes were used for these experiments. The animals were anesthetized with alpha chloralose (60 to 80 mg/kg body weight) and urethan (40 mg/kg). The neck was opened by midline incision and both vagus nerves were isolated high in the neck. The sheath of the vagus was split just below the junction with the superi-

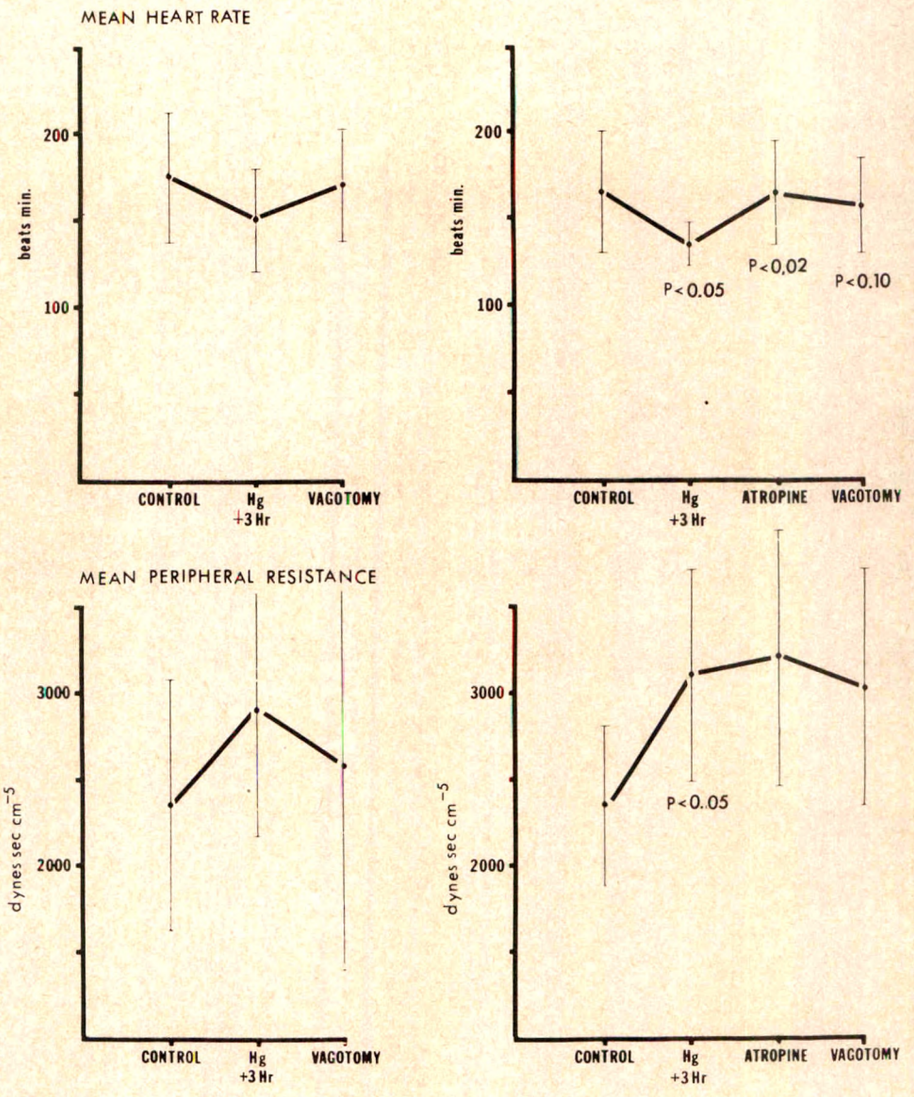

FIGURE 2. Changes in heart rate and peripheral arteriolar resistance in the same seven dogs as in Figure 1.

or laryngeal nerve, and the aortic nerves were carefully isolated on both sides. The aortic nerves were identified by placing them loosely on platinum bipolar electrodes and recording characteristic action potentials. These nerves were not disrupted and care was taken not to damage them. After identification they were immersed in mineral oil. The left carotid artery was dissected and a double catheter was introduced for probing the left coronary artery as previously described.[18] For the recording of postganglionic sympathetic activity, the left kidney was isolated retroperitoneally and postganglionic sympathetic fibers to the kidney were isolated. In two experiments recordings from sympathetic nerve fibers to the spleen were also obtained. The nerve chosen for recording was crushed peripherally by hemostat and was placed on bipolar platinum-iridium electrodes. The entire field was immersed in mineral oil warmed to body temperature. A catheter was advanced through the isolated femoral vein into the right atrium for the injection of dye.

Base-line recordings: For recording of aortic and sympathetic nerve activity, Tektronix 122 preamplifiers were used which were connected to Astrodata amplifiers. For the sympathetic nerve recordings a band pass filter of 80 to 1,000 cycles/sec and for the aortic nerve recordings 80 to 10,000 cycles/sec was used. The recordings were followed visually on the oscilloscope, and nerve activity was identified also by audio technique and then permanent recordings were made by a Honeywell 1507 Visicorder. Sympathetic and aortic nerve activity was quantified by rectifying of the recorded signal, feeding the data into an integrator and using a meaning circuit with a 3 second time constant. Blood pressure was recorded through the carotid artery catheter, the tip of which was in the ascending aorta. Heart rate was calculated from the time interval between the upstrokes of the systolic pressure waves. Cardiac output determinations were performed in duplicate using 2.5 mg indocyanine green dye for each injection through the venous catheter into the right atrium and withdrawing blood by Harvard constant withdrawal pump through a Gilford densitometer. Calculation of cardiac output was performed by the triangulation technique and the results were compared with those obtained simultaneously with a Lexington cardiac output computer. The average of the two sequential cardiac outputs was used in the calculation of the results.

Production of myocardial infarction: Base-line recordings of pressures, aortic and sympathetic nerve activi-

ty, cardiac output and the electrocardiogram were performed in each animal before myocardial infarction was produced. The inner catheter was then advanced into the outer catheter which had previously been passed through the left common carotid artery into the ascending aorta. Under image intensifier the left coronary ostium was entered with the outer catheter. By advancing the inner catheter and injecting small amounts of contrast dye (Hypaque-M®, 75%), it was possible to advance the inner catheter into the circumflex coronary artery as previously described.[18] When the inner catheter was in location, 0.2 ml of metallic mercury was injected through the catheter under image intensifier control into the circumflex coronary artery. The injection was followed by a flush with 1 ml of physiologic saline solution. The inner catheter was then withdrawn and the outer catheter placed into the ascending aorta for later recording of blood pressure and cardiac output. This technique, a modified version of the method of Lluch et al.,[21] was used to produce myocardial infarction in more than 60 previous experiments.[19,20] In those experiments approximately 80 percent of the animals had severe myocardial infarction with shock and low cardiac output within 1 to 4 hours.

Recordings of cardiac output, blood pressure, sympathetic and aortic nerve activity were repeated every 30 minutes after signs of myocardial infarction appeared in the electrocardiogram after the injection of mercury. The nerves were not moved from the electrodes and the animals were kept warm with use of a heating pad during this time. Fluid was replaced by slow infusion of dextrose in saline solution. Repeated small doses of the anesthetic were given as needed.

When cardiac output decreased to approximately 50 percent of control level and blood pressure decreased significantly, which usually occurred within 3 hours after mercury injection, the following interventions were made. In the first group of seven dogs (Group 1), the isolated vagus nerve high in the neck was cut on both sides without cutting the aortic nerves, which had previously been separated from the vagus. In a second group of five dogs (Group 2), atropine was given intravenously (0.1 mg/kg) before the vagus nerves were cut. Recordings were repeated after administration of atropine. Thirty minutes after injection of atropine, the vagus trunks were cut in these animals as in the previous group. All data were calculated as averages of means, and the base-line measurements before infarction were compared with measurements obtained after infarction, after vagotomy alone and after atropine and vagotomy, using each animal as its own control. For statistical analysis of the differences between experimental states (base-line, infarction, infarction plus vagotomy or atropine) the paired *t* test of Snedecor was used.

Results

Cardiac output and arterial blood pressure: Cardiac output and mean systemic blood pressure decreased in both groups of animals after injection of mercury into the circumflex coronary artery as was shown in previous experiments (Fig. 1). The decrease reached about 50 percent of the base-line value 3 hours after injection of mercury. Calculated peripheral resistance simultaneously increased but the increase was less than that expected from the decrease of cardiac output since mean systemic blood pressure also decreased (Fig. 2). Heart rate generally decreased and was 16 percent below control level at 3 hours. However, these changes reached statistical significance only in Group 2 (atropine plus vagotomy). Table I shows the average hemodynamic changes in all experiments.

Aortic nerve activity, sympathetic discharge and cardiac vagal afferent activity: With the decrease in cardiac output and systemic blood pressure, the mean aortic nerve activity also decreased in both groups as expected. But contrary to the expected reflex response under normal physiologic conditions, sympathetic discharge to the kidney was decreased to about 50 percent of the base-line activity despite the baroreceptor withdrawal (Fig. 3 and 4). Since baroreceptor input to the cardiovascular centers from the aortic nerve (and presumably the carotid sinus nerves) was markedly decreased, as shown by the decrease of aortic nerve activity, inhibition of sympathetic drive must have originated in other areas of the cardiovascular system, presumably in the heart itself. This powerful reflex was transmitted through vagal afferents since, when the vagus nerves were cut bilaterally high in the neck (leaving the aortic and carotid sinus nerves intact), there was an immediate increase of mean sympathetic activity in both groups which persisted until termination of the experiment 1 hour after the disruption of the vagus nerves (Fig. 3 and 4). Simultaneously with the increased sympathetic activity, cardiac output and systemic mean blood pressure also increased (Fig. 1). However, the increase reached significance for cardiac output only in Group 1 (vagotomy only) and for blood pressure in Group 2 (atropine plus vagotomy). The change in mean heart rate after cutting the vagus was not significant. Calculated peripheral resistance showed a tendency to decrease, but did not change significantly. Aortic nerve activity increased, reflecting the increase in systemic blood pressure, but this increase did not suffice to inhibit the increased sympathetic drive when the powerful cardiac vagal afferent activity was interrupted.

The responses of renal and splenic sympathetic fiber activity did not differ when compared in the two experiments in which both were recorded. Renal and splenic nerve activity levels were equally suppressed during shock and equally raised after the vagus was cut. However, the number of comparison recordings was insufficient to make a definite determination.

Effect of atropine: In the experiments in which atropine was given intravenously before the vagus was cut, mean sympathetic nerve activity, cardiac output and systemic blood pressure did not increase after administration of atropine, but heart rate significantly increased. (Fig. 1 and 4). When the vagus was subsequently cut bilaterally in these atropinized animals an increase in mean sympathetic nerve activity occurred as well as an increase in cardiac output and systemic blood pressure, thus indicating that atropine blocked only the efferent vagal activity responsible for bradycardia but did not block the central sympathetic inhibition of the afferent vagal reflex originating in the heart. Thus, atropine may have

TABLE 1

Hemodynamic Changes Before and After Myocardial Infarction and After Subsequent Bilateral Vagotomy, and Atropine with Subsequent Vagotomy (means ± standard deviations)

Measurement	Base Line	3 Hours After Mercury Injection and Myocardial Infarction	After Atropine (0.1 mg/kg)	After Bilateral Vagotomy
		Group 1 (Vagotomy Alone, Seven Dogs)		
Mean systemic blood pressure (mm Hg)	108 ± 23.1	83 ± 12.1 $P<0.01$*	...	97 ± 18.4 NS*
Heart rate (beats/min)	185 ± 37.5	163 ± 33.1 NS*	...	178 ± 32.5 NS*
Cardiac output (liters/min)	3.84 ± 0.72	2.53 ± 0.4 $P<0.01$*	...	3.39 ± 0.9 $P<0.02$*
Stroke volume (ml/beat)	20.7 ± 7.5	15.5 ± 4.2 $P<0.01$*	...	19.0 ± 3.8 $P<0.02$*
Peripheral vascular resistance (dynes sec cm^{-5})	2348 ± 720	2723 ± 713 NS*	...	2565 ± 1185 NS*
		Group 2 (Vagotomy Preceded by Atropine, Five Dogs)		
Mean systemic blood pressure (mm Hg)	106 ± 12.4	83 ± 8.6 $P<0.01$*	80 ± 7.0 NS*	93 ± 8.3 $P<0.01$†
Heart rate (beats/min)	164 ± 35	133 ± 11 $P<0.05$*	164 ± 29 $P<0.02$*	157 ± 29 NS*; NS†
Cardiac output (liters/min)	3.66 ± 0.6	2.20 ± 0.3 $P<0.01$*	2.08 ± 0.4 NS*	2.48 ± 0.6 NS†
Stroke volume (ml/beat)	22.3 ± 8.4	16.5 ± 5.1 $P<0.01$*	12.6 ± 6.0 $P<0.02$*	15.8 ± 4.8 $P<0.05$*; NS†
Peripheral vascular resistance (dynes sec cm^{-5})	2374 ± 459	3107 ± 605 $P<0.05$*	3207 ± 743 NS*	3047 ± 681 NS*

* Significance values for differences between values of previous state and those of state under which values are written.
† Significance values for differences between values after bilateral vagotomy and those obtained 3 hours after mercury injection.
NS = not significant; P = probability.

eliminated the vagal efferent component of bradycardia but did not change cardiac performance or redistribution of blood flow. Since the heart rates before and after mercury injection were relatively high, the effect of atropine was also only modest.

Discussion

Considerable evidence has been collected by investigators in recent years that vagal afferents may play a role in the suppressed cardiac function and systemic circulation in certain cardiovascular diseases. Mark et al.[22] have shown in patients with aortic stenosis that syncope after effort may be due to a vagal afferent reflex resulting from distension of the left ventricle. Exercise in patients with aortic stenosis resulted in peripheral venous dilatation rather than constriction, probably as a result of the excessive stimulation of the vagal afferents in the left ventricle. Experimental evidence seemed to substantiate the results in patients.[23] In other experiments using the isolated hind limb preparation with constant flow, Hanley et al.[24] demonstrated that myocardial infarction resulted in decreased rather than increased perfusion pressure as would be expected from the decrease of systemic blood pressure and cardiac output in this condition. The renal vascular bed also showed vasodilatation according to Hanley et al.,[25] and Gorfinkel et al.[26] found only moderate decrease of renal blood flow and production of urine.

Sympathetic and vagal activity after myocardial infarction and effect of vagal block: In our experiments the decrease of sympathetic activity was shown by actual recording of electroneurograms simultaneously with the withdrawal of baroreceptor input demonstrated by reduced aortic nerve activity. Cardiac output and blood pressure decreased simultaneously. The decrease in pressure occurred despite the increase in calculated peripheral resistance. However, the increase in resistance probably does not reflect the state of the peripheral blood vessels. First, some of the increase in resistance is perhaps due to increased circulating catecholamines originating in the adrenal medulla as occurs in myocardial infarction.[27,28] Second, there is probably poor organ perfusion due to the reduced cross-sectional area of the resistance vessels caused by sludging and marked decrease of velocity of circulation through the peripheral vascular system. Thus, peripheral resistance is increased despite decreased central sympathetic drive to the vascular system.

The disruption of the inhibitory reflex originating in the heart results in an increased sympathetic

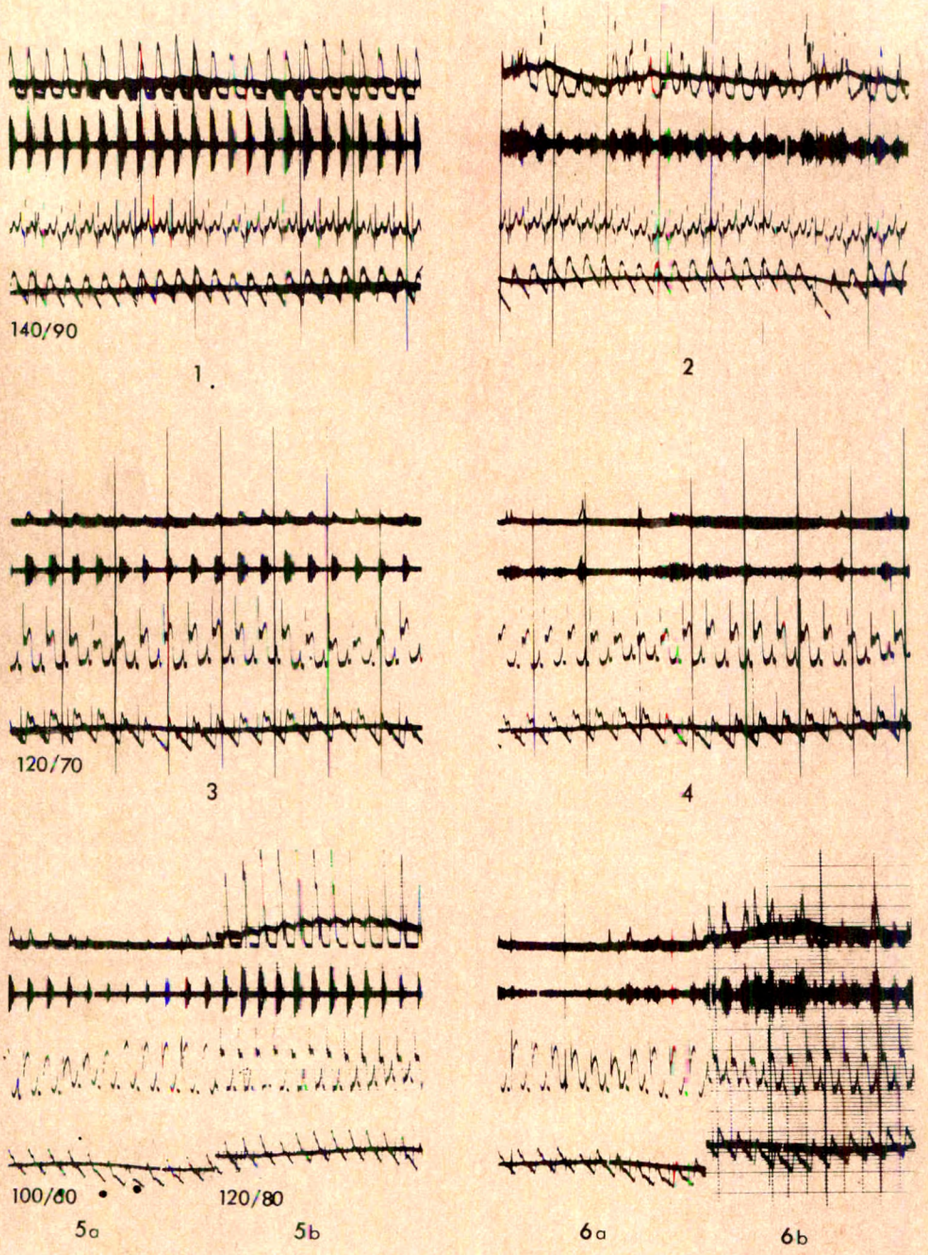

FIGURE 3. Example of aortic nerve **(left panels 1, 3, 5a and 5b)** and postganglionic sympathetic nerve **(right panels 2, 4, 6a and 6b)** activity in one dog before **(panels 1 and 2)** and after 3 hours of myocardial infarction with hypotension and low cardiac output **(panels 3 and 4),** and before **(5a and 6a)** and after **(5b and 6b)** bilateral vagotomy during the 4th hour of shock. In each panel the graphs from bottom to top indicate systemic blood pressure (straight line is mean pressure), electrocardiogram, actual nerve recording, integrated nerve activity (straight line is mean activity). Note the decrease in aortic and sympathetic nerve activity at 3 and 4 hours **(panels 3, 4, 5a and 6a)** and increased activity after vagotomy **(panels 5b and 6b).**

drive, as we could see in our experiments, leading to an increase of cardiac output and probably raising the peripheral pressure above the critical closing pressure in many vascular areas.[29,30] This finding indicates that the vagal afferent reflex actually functions in a reverse manner in myocardial infarction, thereby leading to hypotension, decreased cardiac output and bradycardia and, in some degree, defeats the pressor regulating system by its positive feedback mechanism. With the advance of time the peripheral effects of sludging and slowing of the circulation are so overwhelming that cardiac performance further deteriorates, probably in part because of metabolic depressant factors, and all attempts to improve circulation are of no avail.[31] We have shown in these experiments that, within 3 hours from the onset of myocardial infarction, blocking the vagus or cutting it leads to temporary improvement of cardiac output and probably improvement of the circulation to critical organs. Atropine does not duplicate the effect of vagus block in spite of its effect on heart rate.

Renal blood flow is maintained despite hypotension in coronary occlusion.[25] There is probably a difference in the circulatory adjustment of different vascular beds and their sympathetic drive in shock. However, this may apply more to the sympathetic response to elimination of baroreceptor inhibition than to maximal inhibition itself. Kendrick et al.[32] have

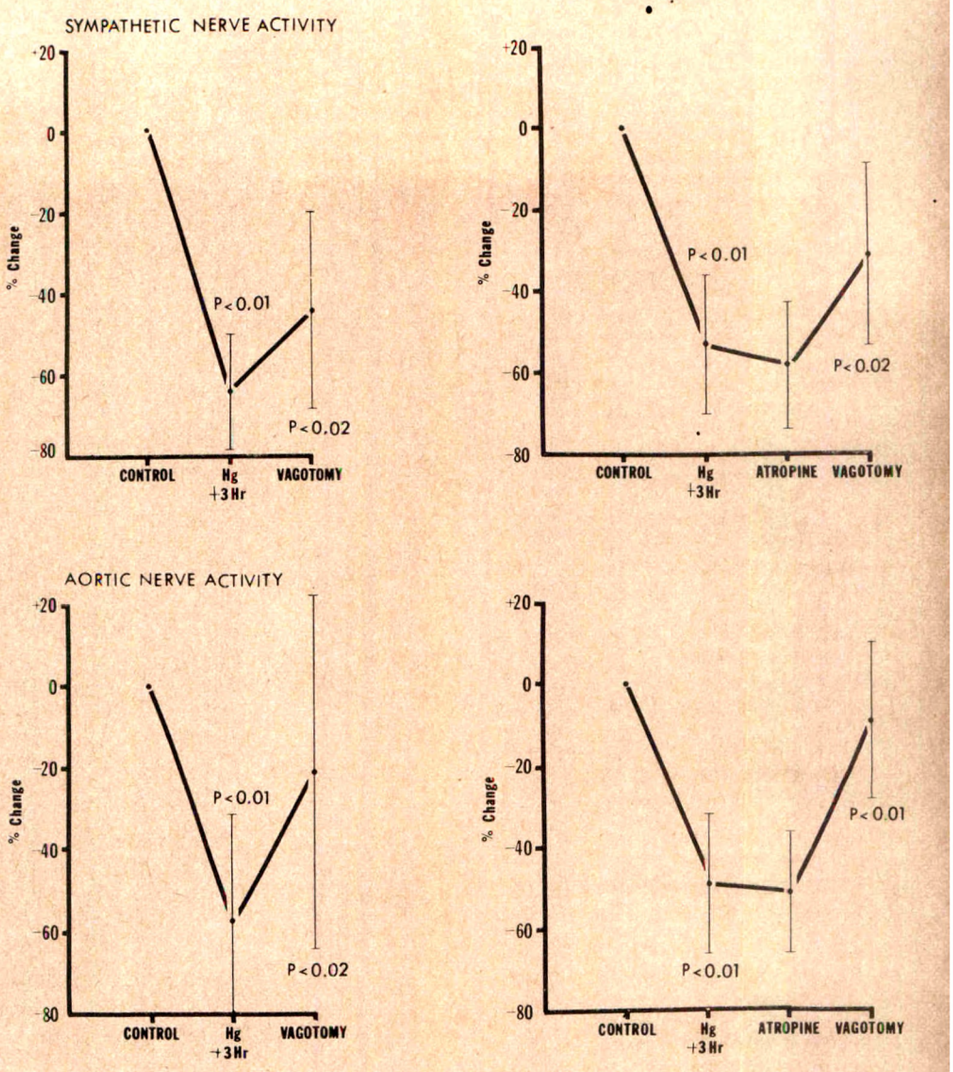

FIGURE 4. Average postganglionic sympathetic and aortic nerve activity changes before and during shock and after vagotomy in seven dogs (Group 1) **(left graphs)** and after atropine and subsequent vagotomy in five dogs (Group 2) **(right graphs)**. The changes are expressed in percent of control. **Horizontal bars** indicate standard deviations. Note the significant lowering of both nerve activity levels during shock and the rise after vagotomy with no increase after atropine.

shown that renal sympathetic activity increased less than activity to the intestine upon withdrawal of baroreceptor inhibition. In our two experiments in which both renal and splenic sympathetic nerve activities were recorded no difference in activity increase was seen after vagotomy. However, the activity only increased to about base-line level. Since the systemic baroreceptors (carotid sinus and aortic nerves) were left intact, no maximal sympathetic activity occurred because it was now inhibited to a certain degree by these baroreceptors. Elimination of systemic baroreceptors, superimposed on vagotomy, would probably have brought out the differences in the maximal sympathetic activity response of the two vascular beds. Nevertheless, a redistribution of sympathetic drive (and blood flow) after vagotomy in our shock experiments can be assumed from other studies.

Clinical implications: Since in man it is not possible to block vagal afferent activity selectively, the alternative is to increase pharmacologically the beta adrenergic sympathetic drive to the heart and the alpha adrenergic drive to the peripheral blood vessels.[20,33] We have found that this type of sympathetic augmentation in cardiogenic shock is most effective when drug combinations are used. Carefully titrated doses of isoproterenol producing beta adrenergic stimulation of the heart will result in increased cardiac output, and the addition of small doses of norepinephrine to supplement the inadequate peripheral sympathetic drive will produce elevation of mean systemic blood pressure to an optimal level. This may result in adequate coronary perfusion pressure, as we have shown in previous experiments.[20] Our approach appeared to compensate for the depressed sympathetic drive to the heart and the peripheral vascular system and to correct the effect of the positive feedback mechanism due to the vagal afferent reflex. Atropine did not lead to improved cardiac output or to increased renal sympathetic activity or, presumably, to advantageous redistribution of blood flow despite its effect of eliminating the relative bradycardia. These findings with atropine are in accord with those of Karsh et al.[34]

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Accumulation of Gallium-67 in Regions of Acute Myocardial Infarction

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The radionuclide gallium-67 has been shown to accumulate in a variety of inflammatory and neoplastic lesions, thereby permitting identification of these abnormalities by radioisotope imaging. We have found that ^{67}Ga also accumulates selectively in recently infarcted myocardium. Acute myocardial infarction was induced in dogs by ligation of the left anterior descending coronary artery, then ^{67}Ga (3 to 4 mc) was injected intravenously. Hearts were removed 24 hours later, and isotope localization was evaluated by an Anger camera and by autoradiography. In five of eight dogs, ^{67}Ga was found to accumulate preferentially in regions of visible infarction. Tissue creatine phosphokinase (CPK), measured in four of the five dogs, was greatly reduced and white blood cell infiltration was intense in the infarcted region. The infarcts of three dogs without preferential ^{67}Ga uptake showed lesser degrees of CPK reduction and white blood cell infiltration. Localization of ^{67}Ga in regions of acute myocardial infarction was also demonstrable by scanning intact, closed chest dogs. Hearts of two animals with transient (20 minutes) ischemia showed neither ^{67}Ga accumulation nor decreased CPK. Thus, ^{67}Ga localization discriminates infarcted from normal or only transiently ischemic myocardium. Unlike potassium and its analogs, ^{67}Ga scanning does not depend on resolution of "cold" areas nor is it likely to introduce ambiguities due to flow limitation of isotope delivery. For these reasons ^{67}Ga may prove particularly useful in the imaging of acute myocardial infarction in man.

It recently has become apparent that radioisotope techniques may offer important assistance in the detection of acute myocardial infarction.[1–13] Myocardial scanning agents currently in use (chiefly radioactive potassium and its analogs) depend on resolution of "cold" areas in which the lack of myocardial isotope uptake is interpreted as an infarcted region. A tracer with the ability to concentrate in infarcted tissue, thereby producing a "hot" area, would have the advantage of improved resolution and ease in interpretation. Moreover, an isotope specifically localizing in regions of acute myocardial infarction would be of particular use in discriminating zones that were merely receiving abnormal perfusion but had no actual tissue injury. This distinction cannot be made with any of the myocardial scanning agents now used.

The radionuclide gallium-67 has attained widespread use as a scanning agent having the capability of localizing in a variety of inflammatory lesions and neoplasms.[14–17] Because an inflammatory process is an intrinsic part of the evolution of acute myocardial infarction, we examined the ability of intravenously administered ^{67}Ga citrate to accumulate selectively in areas of recently infarcted canine myocardium.

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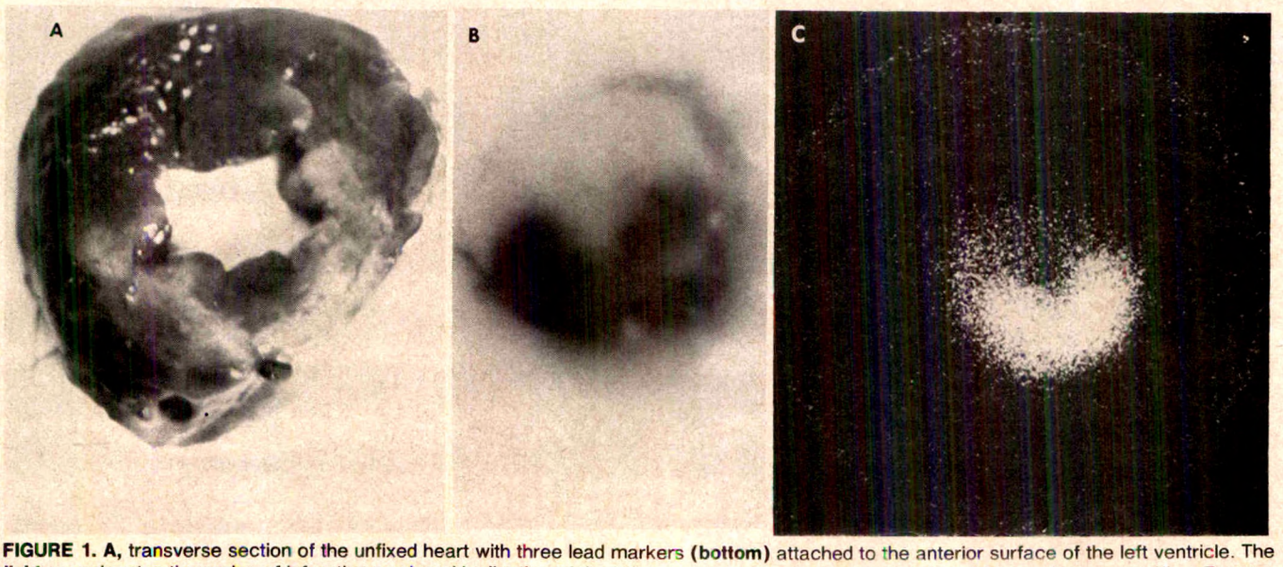

FIGURE 1. A, transverse section of the unfixed heart with three lead markers **(bottom)** attached to the anterior surface of the left ventricle. The **light area** denotes the region of infarction produced by ligation of the left anterior descending coronary artery 24 hours before sacrifice. **B,** autoradiograph of the same section shown in **A,** revealing markedly increased radioisotope uptake **(dark portions)** corresponding to the region of infarction. Lead markers appear as three small filling defects at the **bottom** and **right margin** of the area of increased uptake. **C,** gamma camera study of the same section demonstrating ^{67}Ga accumulation in the infarcted region. Orientation as in **B.**

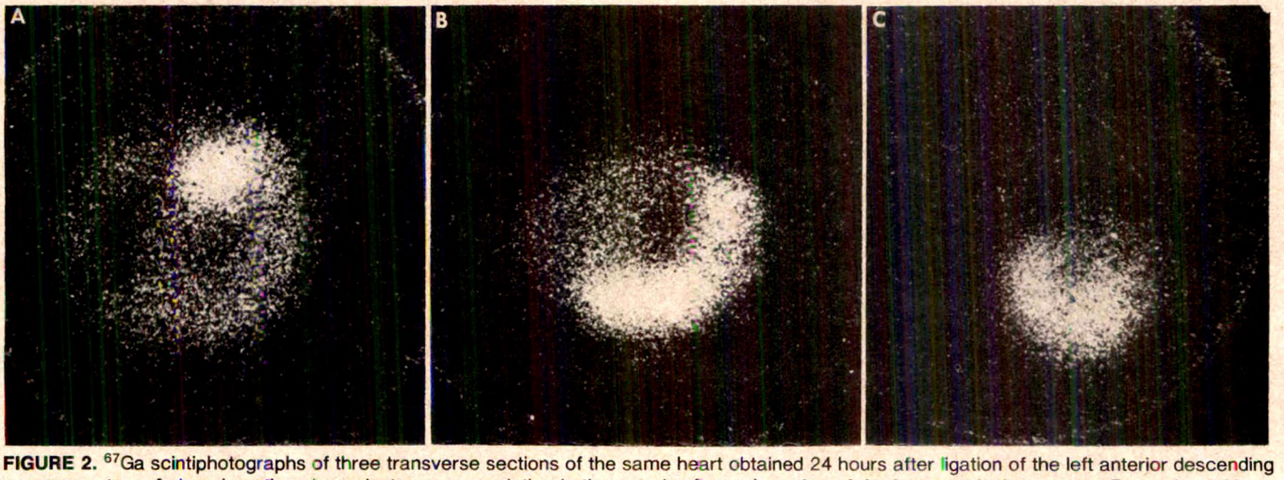

FIGURE 2. ^{67}Ga scintiphotographs of three transverse sections of the same heart obtained 24 hours after ligation of the left anterior descending coronary artery. **A,** basal section shows isotope accumulation in the anterior **(upper)** portion of the interventricular septum. **B,** section midway between apex and base with increased isotope accumulation in anterior **(bottom)** and lateral portions of the left ventricle. **C,** apical section also shows anterior **(bottom)** crescent of ^{67}Ga accumulation.

Methods

Preparation of infarcts: Myocardial infarction was surgically induced in 15 dogs. After sodium pentobarbital anesthesia (30 mg/kg body weight, intravenously), the thorax was entered through a median sternotomy or a left lateral thoracotomy, the pericardium opened, and the left anterior descending coronary artery was ligated at the level of the lower margin of the left atrial appendage. Two control animals underwent 20 minutes of ischemia induced by temporary occlusion of the left anterior descending coronary artery. In one group of dogs (Group I) ^{67}Ga citrate (3 to 4 mc) was given intravenously immediately after operation, and the hearts were removed 24 hours after induction of myocardial infarction or control ischemia. The excised hearts were then studied with a scintillation camera and autoradiography; portions of infarcted and noninfarcted tissue were taken for histologic sections and tissue creatine phosphokinase (CPK) assay. A second series of animals (Group II) underwent surgical infarction, then were scanned in vivo 2, 3 and 4 weeks after infarction with 3 to 4 mc ^{67}Ga citrate given intravenously 24 to 48 hours before each scan.

Histologic and enzymatic studies: Myocardial infarction was documented by histologic sections of extirpated hearts and by tissue CPK assay. Histologic sections were stained with hematoxylin-eosin. Particular attention was

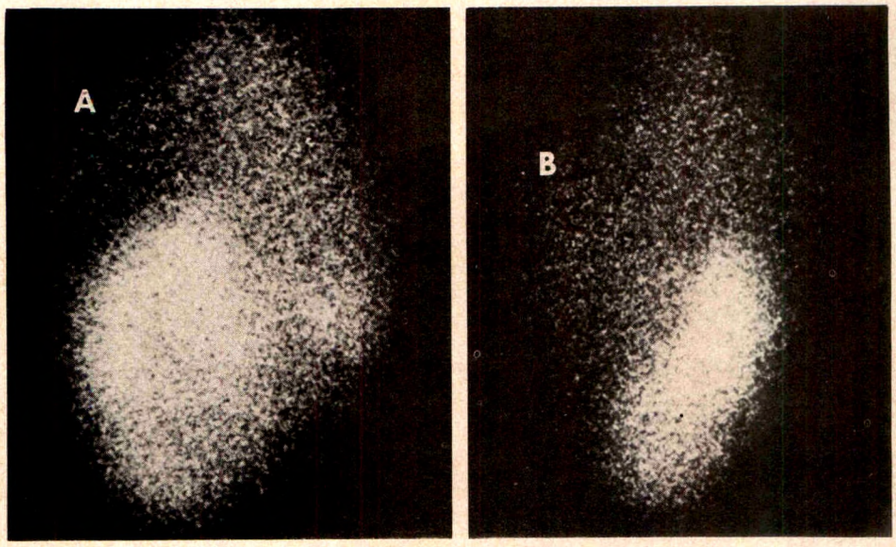

FIGURE 3. ^{67}Ga scintiphotographs of the whole excised heart 24 hours after infarction produced by ligation of the left anterior descending coronary artery. **A,** anterior view reveals a region of increased isotope accumulation extending along the interventricular groove **(sharply demarcated left margin)** nearly to the apex **(bottom). B,** left lateral view confirms the anterior **(rightward)** and apical **(bottom)** location of increased ^{67}Ga uptake corresponding to the anteroapical site of the infarct.

paid to degree of inflammatory cell infiltration in sections from both infarcted and noninfarcted regions. CPK assay was performed on full thickness punch biopsy specimens taken from both grossly normal and infarcted tissue. The tissue was prepared and assayed according to previously published techniques.[18] The range for normal tissue is 700 to 1,000 international units/mg wet weight.

Autoradiography: Autoradiography was performed by placing fresh or formalin-fixed 1 to 2 cm thick horizontal slices of the entire extirpated heart on Kodak medical X-ray film, then storing in total darkness at 0° C. The film was exposed to the tissue for 1 to 3 days and subsequently developed in a standard X-ray processing unit.

Scintigraphic technique: Isotope localization was determined in intact animals, extirpated whole hearts and transverse sections of whole hearts (perpendicular to the interventricular septum) with a Nuclear-Chicago Pho/Gamma High Performance scintillation camera using a large bore pinhole collimator. To form each image, 250,000 to 900,000 counts were collected for intact animals and 50 to 150,000 counts were accumulated for extirpated hearts and tissue slices. In all studies maximal sensitivity of gamma detection was set at 190 kev with a 35 percent window to encompass the 184 kev photopeak of ^{67}Ga.

All myocardial isotope scintigraphic data were analyzed with a Hewlett Packard Computer 5407A Scintigraphic Data Analyser. The raw data were stored in digital form on magnetic tape. Standard computer programs were used to subtract background counts and frame the raw data into images.

Extirpated hearts were imaged from both the anterior and lateral aspects. Intact animals were scanned in the left lateral position while sedated with diazepam and sodium pentobarbital. To further localize areas of isotope accumulation within the myocardium, a double isotope procedure was used in several animals. In these studies, the ^{67}Ga scintigraphic image was first stored on the 5407A computer system. Without moving the animal, a bolus of ^{99m}technetium-labeled albumin or ^{99m}technetium sulfur colloid was injected intravenously. The initial passage of the isotope through the heart was recorded and an image of the cardiac blood pool was made.

TABLE I

Correlation of Gallium-67 Localization with Tissue CPK and Myocardial Histologic Features

		Histologic Features	
^{67}Ga Localization	Tissue CPK (% of control)	MI	WBC Infiltration
Good visualization	...	+	+
Good visualization	11%	+	+
Good visualization	15%	+	+
Fair visualization	19%	+	±
Fair visualization	35%	+	−
Poor visualization	40%	+	−
Poor visualization	45%	+	−
Poor visualization	46%	+	−
No visualization*	90%	−	−
No visualization*	95%	−	−

* Transiently ischemic.

CPK = creatine phosphokinase; MI = myocardial infarction; WBC = white blood cell; ... = not performed; − = absent; + = present; ± = marginally present.

Results

Acute studies in extirpated hearts (Group I): Scintigrams and radioautographs of hearts extirpated 24 hours after coronary ligation and ^{67}Ga administration revealed localization of the isotope in the region of myocardial infarction. Studies of horizontal sections showed sharply delineated regions of ^{67}Ga uptake corresponding closely to portions manifesting grossly evident infarction (Fig. 1). Noninfarcted regions did not accumulate ^{67}Ga. The tendency of ^{67}Ga to accumulate selectively within infarcted tissue permits scintigraphic mapping of the extent of the infarction produced by coronary ligation (Fig. 2). The

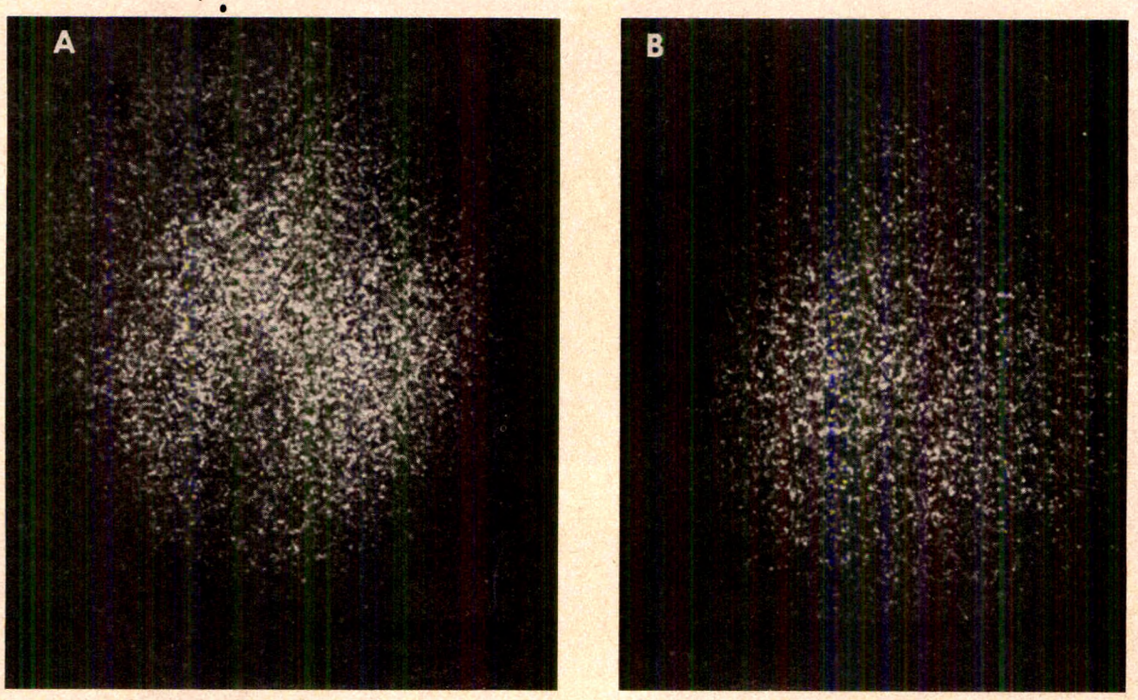

FIGURE 4. ^{67}Ga scintiphotographs of the whole excised heart 24 hours after ischemia induced by a 20 minute period of occlusion of the left anterior descending coronary artery. In contrast to Figure 3, no area of increased isotope uptake is observed. **A,** anterior view, orientation as in Figure 3A. **B,** left lateral view, orientation as in Figure 3B.

region of myocardial infarction was also delineated by anterior and lateral scintigrams of the whole extirpated heart (Fig. 3). In contrast, anterior and lateral scintigrams of extirpated hearts subjected to a 20 minute period of anterolateral ischemia 24 hours before study manifested no tendency for ^{67}Ga localization (Fig. 4). Lack of myocardial infarction in these two hearts in which ^{67}Ga was not selectively taken up was confirmed by enzymatic and histological studies (Table I).

Adequate scintigraphic evidence of ^{67}Ga localization was observed in five of eight extirpated hearts studied 24 hours after coronary ligation (Table I). Each of these hearts manifested histologic and enzymatic evidence of myocardial infarction. Scintigraphic evidence of ^{67}Ga localization was seen in those five hearts with the greatest severity of ischemic injury, as assessed by CPK reduction. Moreover, the three hearts with the most intense ^{67}Ga localization also demonstrated dense polymorphonuclear leukocyte infiltration of the infarcted region on histologic section. Conversely, this degree of ^{67}Ga accumulation was not seen in the absence of dense leukocyte infiltration.

Chronic studies in intact animals (Group II): When ^{67}Ga was injected 24 to 48 hours before study, adequate scintigraphic visualization of a region of ^{67}Ga uptake was obtained in the intact dog. As shown in Figure 5, radioisotope labeling of the cardiac blood pool demonstrated that this region of ^{67}Ga localization corresponds to the anterior and apical location of the surgically induced myocardial infarction. Accumulation of ^{67}Ga also was seen in areas of surgical scar. However, the region of myocardial infarction was readily distinguished from surgical scar by its proximity to the cardiac blood pool in multiple projections. Moreover, the scintigraphic appearance

TABLE II

Time Course of ^{67}Ga Uptake in Myocardial Infarcts

Dog no.	Weeks 1	2	3	4
1	+	+	+	−
2	+	+	+	−
3	+	+	−	−
4	+	+	−	−
5	+	+	+	...
6	+	+	+	...
7	+	+	...	...
8*	−	−	−	...
9†	+	+	+	...

* Control animal.

† Control animal with severe pericarditis.

... = scintigram not obtained, − = negative scintigram; + = positive scintigram.

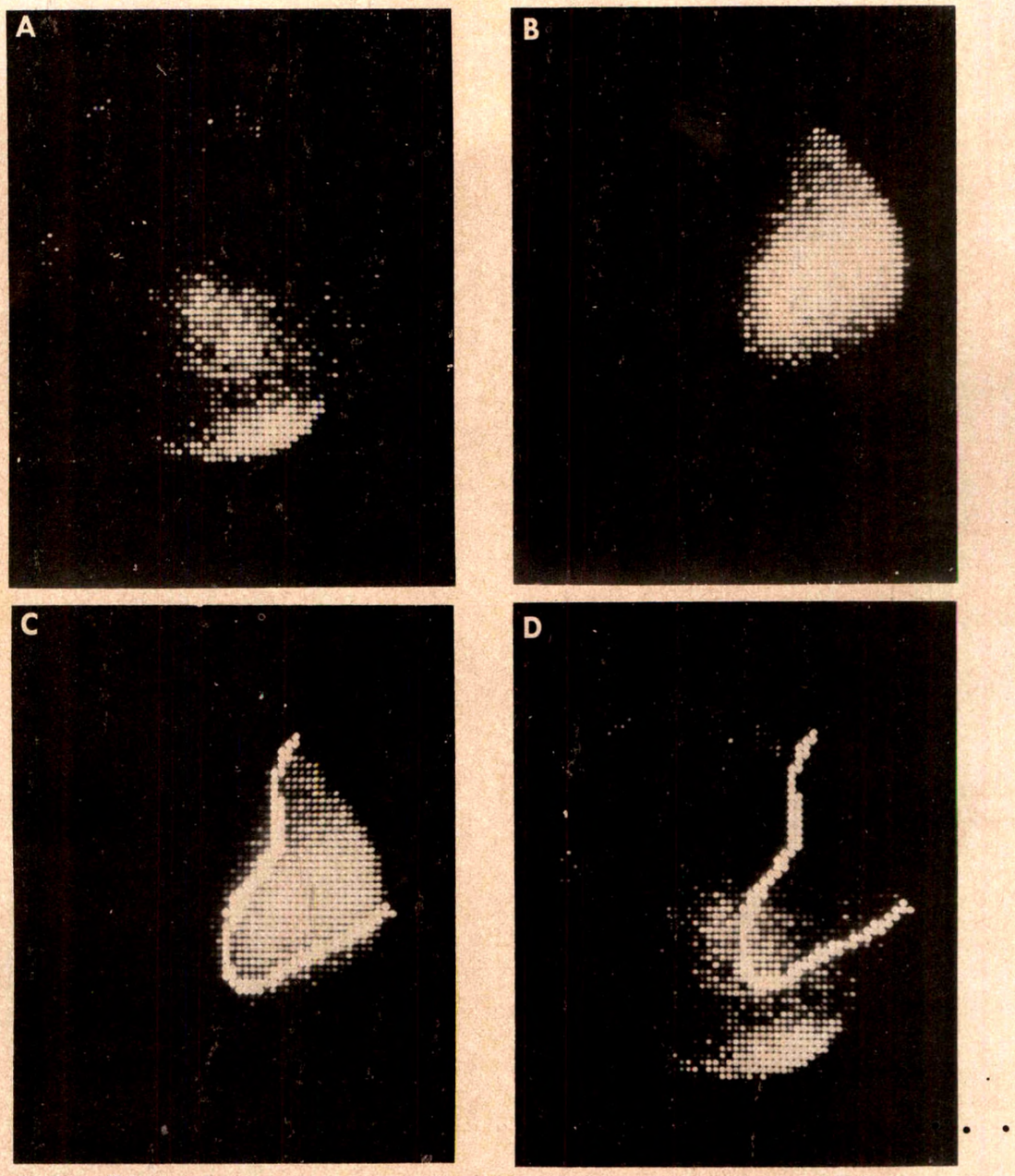

FIGURE 5. A, left lateral ^{67}Ga scan of the chest of the intact dog 24 hours after ligation of the left anterior descending coronary artery (anterior chest to the **left**). Isotope localization is seen in the region of the heart **(center)** and liver **(bottom).** Isotope localization over the heart was not seen in sham-operated animals. **B,** left lateral scan of the cardiac blood pool was made after injecting ^{99m}Tc-albumin without moving either animal or gamma camera. Orientation as in **A. C,** an outline of the cardiac blood pool was made from the scan shown in **B** using a computer-linked "light pen." **D,** computer superimposition of the outline of the cardiac blood pool **(C)** on the ^{67}Ga scan **(A)** documenting anteroapical isotope uptake, corresponding to the site of infarction.

of ^{67}Ga localization in the region of myocardial infarction was similar whether the associated surgical scar resulted from left lateral thoracotomy or from midline thoracotomy.

Scans were obtained repeatedly after coronary ligation to evaluate the length of the postinfarction period during which ^{67}Ga localization was demonstrable. Because of the short half-life of ^{67}Ga (78 hours), no detectable isotope remained in the heart at the time of repeat administration of ^{67}Ga. As shown in Table II, all seven of the animals scanned at 2 or 3 weeks had positive scintigrams but none of the four animals studied at 4 weeks showed evidence of ^{67}Ga localization although each had had a positive scintigram 1 or 2 weeks previously. In each of these latter four dogs, absence of ^{67}Ga localization was confirmed

by scintigrams of the extirpated heart. Thus, in our animal model, myocardial infarction could be demonstrated by ^{67}Ga accumulation for a period of approximately 3 weeks after the ischemic insult.

In one control animal there was no evidence of ^{67}Ga localization in the vicinity of the heart. Isotope localization was observed in a second control animal, but this animal also had severe postoperative pericarditis.

Discussion

Our results indicate that ^{67}Ga accumulates selectively in freshly infarcted canine myocardium, thus permitting scintigraphic delineation of infarction in both extirpated hearts and in the hearts of intact animals. The intensity of ^{67}Ga uptake correlates with the severity of the ischemic damage and, in particular, with the density of polymorphonuclear leukocyte infiltration. This finding is consistent with the results of other investigators suggesting in vivo ^{67}Ga localization in activated neutrophils and histocytes[19–21] and suggests that ^{67}Ga enters or is retained within the infarcted region as a result of the inflammatory cell response to the ischemic tissue damage. This possibility is also supported by our finding that infarcted myocardium will accumulate ^{67}Ga for only about 3 weeks after the initiating ischemic insult, a time period comparable to the duration of the granulocyte and histocyte invasion of damaged myocardium.[22]

Advantages of method: Radioactive gallium may offer certain unique advantages in the scintigraphic localization and quantification of myocardial infarction. Because of its presumed relation to the biologic properties of ischemic damage, ^{67}Ga localization may be much more specific for regions of acute myocardial infarction than isotope techniques that primarily delineate the nature of coronary flow or the locus of tissues capable of active ion transport. Thus, in addition to recently infarcted tissue, the latter techniques will also yield "cold" areas corresponding to inadequately perfused myocardium (areas of ischemia but not necessarily infarction) and regions of old myocardial scar. Similarly, the presumed dependence of ^{67}Ga localization on cellular migration rather than coronary flow may allow more precise definition of the area of infarct. From a purely physical standpoint, a positive scan may offer greater resolution than a technique relying on the identification of "cold" regions. Since ^{67}Ga, which appears specific for areas of infarction, differs so completely from radioactive potassium and its analogs, which identify areas of poor perfusion, it is possible that maximal information may be obtained by combining these techniques.

Drawbacks of method: In addition to suggesting the potential utility of ^{67}Ga, our studies also indicate possible drawbacks in ^{67}Ga scanning for myocardial infarction. Only five of eight hearts with documented infarction had ^{67}Ga uptake. Thus, the apparent dependence of ^{67}Ga accumulation on an associated inflammatory cell response may render this technique relatively insensitive. Furthermore, the tendency of ^{67}Ga to accumulate in reticuloendothelial elements of liver and bone marrow[23] may introduce ambiguities into regions of the scan where these tissues are adjacent to the left ventricle. This is particularly likely in evaluating the diaphragmatic surface of the heart, which lies very near the region of the liver. The failure of mercury-labeled chlormerodrin in human trials[24] despite the promising results in experimental animals[2,25] also demonstrates that extrapolation from the experimental situation must always be made with caution.

Nevertheless, previous experience has shown that ^{67}Ga scanning is a safe and effective noninvasive method for evaluating patients with neoplastic and inflammatory disease. Our data suggest that ^{67}Ga photoscanning should be evaluated as a technique for the identification and localization of acute myocardial infarction in man.

Acknowledgment

We are grateful for the operative skill of Mr. Richard McGill and for the dedicated postoperative care of Terry Pitts, DVM, and his associates.

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Dimensional Changes of the Left Ventricle During Acute Pulmonary Arterial Hypertension in Dogs

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Left ventricular dimensions and volumes were measured by an endocardial marker technique in eight closed chest dogs during progressive increases of 10 mm Hg in mean pulmonary arterial pressure. Right ventricular volumes were measured by biplane cineangiography.

Increasing mean pulmonary arterial pressure caused a progressive increase in right ventricular volume; at a mean pulmonary arterial pressure of 60 mm Hg, right ventricular end-diastolic volume increased by 48 percent and end-systolic volume by 50 percent. Left ventricular volumes began to decrease significantly at a mean pulmonary arterial pressure of 30 mm Hg, and when a mean pulmonary arterial pressure of 60 mm Hg was reached, left ventricular end-diastolic volume had decreased by 30 percent and left ventricular end-systolic volume by 19 percent. Changes in ventricular filling pressure directionally followed the volume changes of the respective ventricle. Left ventricular stroke volume decreased 45 percent at a mean pulmonary arterial pressure of 60 mm Hg but increasing heart rate prevented a decrease in cardiac output.

The decrease in left ventricular volume as pulmonary arterial pressure was increased was associated with a disproportionate reduction in the left ventricular septal-lateral axis. At end-diastole, this dimension decreased by 22 percent at a mean pulmonary arterial pressure of 60 mm Hg, the anterior-posterior axis decreased by 8 percent and the base-apex axis by 4 percent. A similar disproportionate decrease of the septal-lateral axis occurred at end-systole. Even at the modest increase in mean pulmonary arterial pressure to 20 mm Hg, only the septal-lateral dimension was significantly shortened, and the right ventricular end-diastolic volume had increased by 17 percent but left ventricular end-diastolic volume was not significantly changed. Thus, during acute pulmonary hypertension, the right ventricle progressively dilates resulting in a distinctive change in the shape of the left ventricle that suggests septal bulging and that may impair left ventricular function.

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*This study was completed during the tenure of Dr. Stool as a Postdoctoral Fellow supported by National Heart and Lung Institute Training Grant HL 05812 and† during the tenure of Dr. Mullins as a Teaching Scholar of the American Heart Association, Inc.

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Alterations in the function of the left ventricle have been observed to occur with primary right ventricular overload states. Patients with cor pulmonale without evidence of other associated heart disease have been shown to have increased left ventricular end-diastolic and pulmonary capillary wedge pressures or depressed left ventricular function curves, or both.[1,2] Increased left ventricular filling pressure has been observed in experimental animals subjected to acute right ventricular overload states.[3,4]

That the mechanical effect of right ventricular distension on the cavity of the left ventricle may affect left ventricular function has been subsequently suggested by studies demonstrating alterations of passive ventricular pressure-volume relations by the degree of filling of the opposite ventricle.[5,6] Matching filling pressures during passive

distension of isolated hearts with those obtained in in vivo volume-loaded hearts, Taylor et al.[6] showed that the distensibility of either ventricle was decreased proportionately to the filling of the opposite chamber and suggested that this phenomenon was secondary to both ventricles sharing a common septum and fiber bundles.

The purpose of this study was to investigate any alteration in left ventricular dimensions that might accompany left and right ventricular volume changes in the intact animal subjected to acute pulmonary hypertension.

Materials and Methods

Eight mongrel dogs weighing between 17 and 25 kg were anesthetized with pentobarbital sodium (15 mg/kg body weight intravenously) and placed on a Harvard respirator pump. A left lateral thoracotomy was performed, and six lead beads were positioned near the left ventricular endocardium to delineate the major and two minor axes of an assumed ellipsoidal shell of muscle adjacent to the left ventricular cavity according to the method of Mitchell and coworkers.[7-9] The distance between the base and apex beads defines the base-apex axis (L_1), that between the anterior and posterior beads is the anterior-posterior axis (L_2) and that between the septal and lateral beads is the septal-lateral axis (L_3). After bead placement the pericardium was loosely reapposed and the thoracotomy closed.

The movements in space between the three pairs of beads were calculated from biplane cinefluorographic exposures taken on 35 mm film at intervals of 1/60 second. Measurements of the spatial lengths of the three axes in the anteroposterior and lateral projections were made from the 35 mm film on a specially modified digitizing system. A cinefluorographic film of a 30 mm steel ball was photographed at the same position as the left ventricle and used to correct for magnification and distortion. Left ventricular volume was calculated by inserting the three ventricular dimensions (L_1, L_2 and L_3) into the formula for the volume of a nonprolate ellipsoid:

$$\text{Volume} = \tfrac{4}{3}\pi abc$$

where $a = L_1/2$, $b = L_2/2$ and $c = L_3/2$.

All calculations were performed on a digital minicomputer using paper tape input and teletype output. All volume and dimensional data represent the mean values of measurements of three representative beats at each value for mean pulmonary arterial pressure.

After a minimum of 3 weeks after bead placement each dog was preanesthetized with morphine sulfate (3 mg/kg body weight subcutaneously), anesthetized with pentobarbital sodium 30 minutes later (15 mg/kg intravenously), intubated and placed on a Harvard respirator. Fluid-filled catheters were positioned by way of peripheral vessels into the left ventricle (National Institutes of Health, no. 8F), right ventricle (Gensini, no. 8F) and ascending aorta (Cournand, no. 8F); a triple lumen balloon catheter (Dotter-Lukas, no. 8F) was positioned in the main pulmonary artery. All pressures were measured with Statham P23Db transducers and recorded with the electrocardiogram and cinefluorographic frame marker on a multichannel photographic recorder (Electronics for Medicine DR-8) at a paper speed of 100 mm/sec. Cardiac output determinations were made by injecting indocyanine green dye into the pulmonary artery and sampling from the aorta using a Harvard withdrawal pump and a Beckman densitometer.

With the balloon catheter deflated, control biplane cinefluorographic films of the left ventricle and simultaneous pressures were recorded immediately after determination of cardiac output by indicator-dilution technique. This sequence was then repeated as the pulmonary arterial balloon was progressively inflated so as to achieve 10 mm Hg increments in mean pulmonary arterial pressure from 20 to 60 mm Hg. After each increment in mean pulmonary arterial pressure approximately 10 minutes was allowed for stabilization of hemodynamic variables. Arterial blood gas levels were determined immediately before each study and monitored frequently throughout the study. The rate and depth of respiration were changed and supplemental oxygen utilized as necessary to maintain appropriate arterial pH, PCO_2 and PO_2 values.

After completion of the left ventricular dimension studies, the pulmonary arterial balloon was deflated for approximately 30 minutes. It was then inflated sequentially exactly as before, but biplane cineangiograms of the right ventricle in the posteroanterior and lateral views were taken at a rate of 60 frames/sec immediately after pressure measurements at each level of mean pulmonary arterial pressure. The angiography was performed under a pressure of 200 lb/sq. in. utilizing a Cordis injector and with 1 ml/kg of Renografin 76® contrast medium. Recordings were made simultaneously of pressures, electrocardiogram and cinefluorographic frame markers. The end-systolic and end-diastolic cinefluorographic frames were traced and used to calculate right ventricular volumes by the longest measured length method of Dodge, which has proved to be an accurate method of measurement of right ventricular volume.[10,11]

Results

Hemodynamics: Table I shows the mean hemodynamic data for the eight dogs, and Figure 1 shows the influence of increasing mean pulmonary arterial pressure on heart rate, aortic pressure and right ventricular and left ventricular pressures. Each point on the individual graphs represents the mean value for eight dogs and the brackets indicate ±1 standard error of the mean. Heart rate began to increase significantly at a mean pulmonary arterial pressure of 40 mm Hg ($P < 0.01$) reaching a maximum at 60 mm Hg. Mean aortic pressure increased slightly from control level at a pulmonary arterial pressure of 50 mm Hg ($P < 0.025$) and decreased at a mean pulmonary arterial pressure of 60 mm Hg to a value not significantly different from control level. The aortic diastolic pressure increased progressively with increasing pulmonary hypertension to a peak at a mean pulmonary arterial pressure of 50 mm Hg ($P < 0.02$) and decreased slightly toward the control value at a mean pulmonary arterial pressure of 60 mm Hg. Systemic vascular resistance, not illustrated, increased very slightly with increasing mean pulmonary arterial pressure from a control value of 3,510 dynes sec cm^{-5} to 4,230 dynes sec cm^{-5} at a mean pulmonary arterial pressure of 60 mm Hg; this change was not statistically significant.

Right ventricular peak systolic and end-diastolic pressures increased progressively as mean pulmonary arterial pressure increased. Left ventricular peak systolic pressure rose slightly from control level at a

TABLE I

Hemodynamic and Left Ventricular Volumes with Increasing Pulmonary Arterial Hypertension

Mean PA Pressure	HR	SV*	CO*	MAP	SVR	Peak LVP	LVEDP	Peak RVP	RVEDP	LVEDV	LVESV	SV	EF
C 12.0	75	31	2.3	105	3511	129	7	31	4	69	37	32	0.46
SE 0.8	4	2	0.19	3	345	8	0.7	2	0.4	30	3	2	0.02
20	78	29	2.3	108	3732	132	6	45	6	67	36	31	0.46
SE 0.4	6	3	0.17	3	343	4	0.7	2	0.6	30	3	2	0.02
†$P<$	NS	NS	NS	NS	NS	NS	NS	0.001	0.05	NS	NS	NS	NS
30	82	28	2.3	112	3794	135	6	61	7	64	35	29	0.45
SE 0.3	6	3	0.19	2	357	3	0.8	3	0.8	3	3	2	0.03
$P<$	NS	NS	NS	NS	NS	0.02	NS	0.001	0.02	0.001	0.05	0.005	NS
40	103	25	2.6	111	3525	135	5	75	8	60	32	28	0.47
SE 0.1	9	3	0.25	3	508	3	0.5	3	0.8	3	3	2	0.03
$P<$	0.01	0.005	NS	NS	NS	0.05	0.02	0.001	0.01	0.001	0.005	0.005	NS
50	135	19	2.5	115	3803	131	4	89	10	55	33	22	0.40
SE 1.2	10	3	0.33	3	536	5	0.4	3	1	3	2	2	0.04
$P<$	0.001	0.001	NS	0.025	NS	NS	0.005	0.001	0.005	0.001	0.01	0.001	0.05
60	170	12	2.1	107	4230	125	3	100	10	48	30	18	0.38
SE 0.6	15	3	0.32	4	582	5	0.5	3	1.2	3	2	2	0.04
$P<$	0.001	0.001	NS	NS	NS	NS	0.001	0.001	0.005	0.001	0.001	0.001	0.01

* Cardiogreen indicator-dilution values.

† Paired Student *t* test with control.

C = control; CO = cardiac output (liters/min); EF = ejection fraction (stroke volume/end-diastolic volume); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDV = left ventricular end-diastolic volume (cc); LVESV = left ventricular end-systolic volume (cc); LVP = left ventricular pressure (mm Hg); MAP = mean arterial pressure (mm Hg); NS = not significant; *P* = probability; PA = pulmonary arterial pressure (mm Hg); RVEDP = right ventricular end-diastolic pressure (mm Hg); RVP = right ventricular pressure (mm Hg); SE = standard error of the mean; SV = stroke volume (cc); SVR = systemic vascular resistance (dynes sec cm^{-5}).

mean pulmonary arterial pressure of 30 mm Hg (P <0.02) and then fell to a level not significantly different from the control value at mean pulmonary arterial pressures of 50 and 60 mm Hg. Left ventricular end-diastolic pressure began to decrease significantly at a mean pulmonary arterial pressure of 40 mm Hg.

Left ventricular volumes: Table I shows the mean data for the changes in left ventricular volume for the eight dogs, and Figure 2 shows the effect of acute increments in mean pulmonary arterial pressure on mean left ventricular volume. Left ventricular end-diastolic volume began to decrease significantly at a mean pulmonary arterial pressure of 30 mm Hg and was reduced by 30 percent at a mean pulmonary arterial pressure of 60 mm Hg (P <0.001). Left ventricular end-systolic volume decreased progressively to 19 percent at a mean pulmonary arterial pressure of 60 mm Hg (P <0.001). Left ventricular stroke volume decreased to 45 percent at a mean pulmonary arterial pressure of 60 mm Hg (P <0.001). Cardiac output did not change significantly in response to progressive pulmonary hypertension, being maintained by increasing heart rate until cardiovascular collapse occurred at mean pulmonary arterial pressures greater than 60 mm Hg. Left ventricular ejection fraction remained unchanged until a mean pulmonary arterial pressure of 50 mm Hg was reached and then began to decrease.

Left ventricular axis lengths: Table II shows the mean data for the changes in individual axis lengths for the eight dogs, and Figure 3 shows the effect of increasing mean pulmonary arterial pressure on the L_1, L_2 and L_3 axis lengths at end-diastole and end-systole, as well as the degree of shortening (axis length at end-diastole minus the axis length at end-systole). At end-diastole the septal-lateral axis (L_3) decreased 23 percent from the control value at a mean pulmonary arterial pressure of 60 mm Hg (P <0.001), whereas the anterior-posterior (L_2) and base-apex (L_1) axes decreased 8 and 4 percent, respectively. At each level of mean pulmonary arterial pressure above the control level, the L_3 axis at end-diastole was significantly smaller than the L_2 or L_1 axis (P <0.001).

At end-systole (Fig. 3), the L_3 axis decreased 15 percent from the control value at a mean pulmonary arterial pressure of 60 mm Hg (P <0.001); the L_2 and L_1 axis lengths at end-systole did not significantly change in response to increasing mean pulmonary arterial pressure. The total axis excursion or degree of systolic shortening of the L_3 axis decreased 53 percent from the control value at a mean pulmonary arterial pressure of 60 mm Hg; the L_2 and L_1 axes were reduced by 20 and 25 percent, respectively.

Right ventricular volumes: Table III shows the mean data for changes in right ventricular volumes. Right ventricular end-diastolic and end-systolic vol-

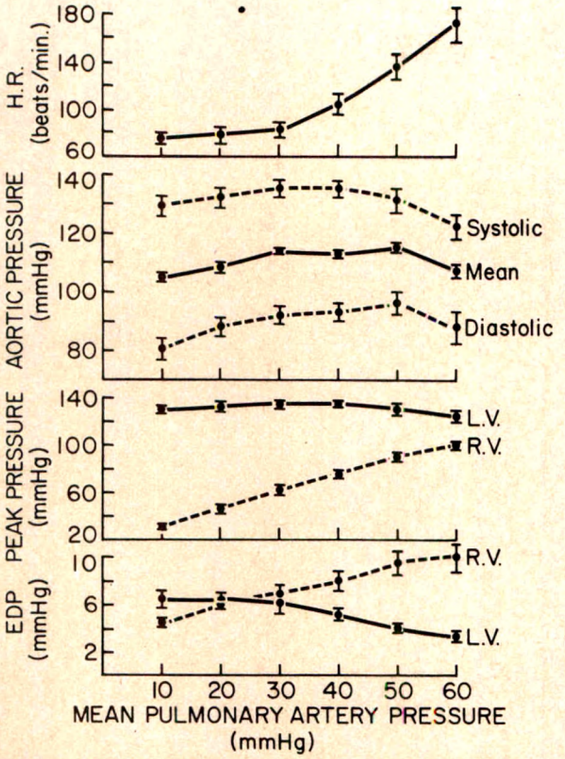

FIGURE 1. Effect of progressive pulmonary hypertension on hemodynamics. Each point represents the mean value for eight dogs and brackets represent the standard error of the mean. EDP = end-diastolic pressure; H.R. = heart rate; L.V. = left ventricle; R.V. = right ventricle.

umes increased approximately 50 percent from control values at a mean pulmonary arterial pressure of 60 mm Hg. Total stroke volume increased from 22 ml during the control period to 32 ml at a mean pulmonary arterial pressure of 60 mm Hg. Data on forward stroke volume were not obtained in this study, but in previous work marked tricuspid regurgitation was noted.[12] Right ventricular ejection fraction remained essentially unchanged.

Discussion

Hemodynamic Effects of Acute Pulmonary Hypertension

In this study the maximal mean pulmonary arterial pressure tolerated by anesthetized dogs subjected to acute balloon-induced pulmonary hypertension was 60 mm Hg. Exceeding this level or holding it for any prolonged period of time resulted in rapid deterioration, which appeared to be related to an inability to further increase heart rate in response to decreasing left ventricular stroke volume. This deterioration was signaled by a sudden reduction in heart rate or mean aortic pressure, or both. This sudden deterioration was usually reversible when the balloon was immediately deflated; when deflation was delayed, the animals were often unable to tolerate lesser degrees of pulmonary hypertension during subsequent attempts to increase pulmonary arterial pressure sequentially.

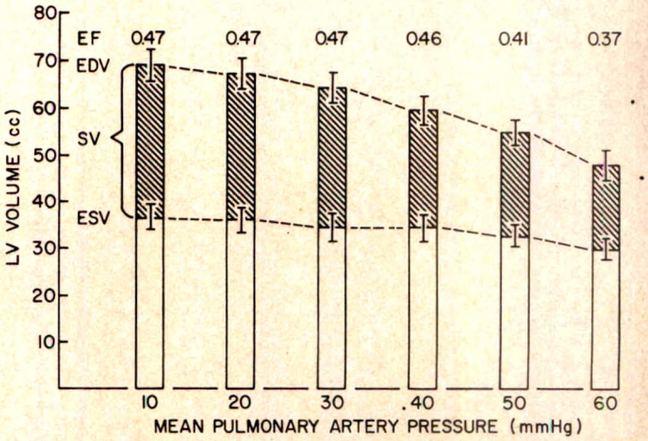

FIGURE 2. Effect of progressive pulmonary hypertension on left ventricular volumes. Volumes represent mean data from eight dogs and brackets represent the standard error of the mean. EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; SV = stroke volume.

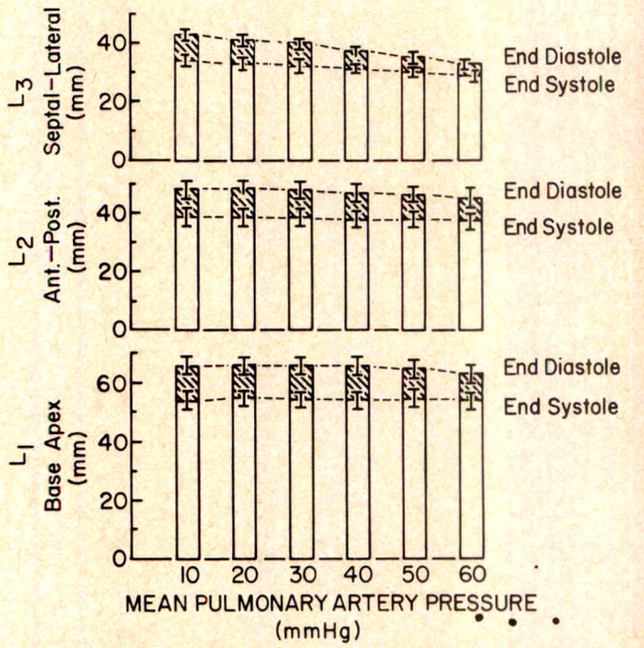

FIGURE 3. Effect of progressive pulmonary hypertension on individual left ventricular axis lengths at end-diastole and end-systole. The **shaded** area of each bar represents the shortening of each axis during systole. L_1 = base-apex length; L_2 = anterior-posterior length; L_3 = septal-lateral length.

This finding may reflect the combined effects of time and stress on our closed chest animals or may represent some as yet undefined structural alteration secondary to acute severe and sustained right ventricular pressure overload.

Laks et al.[13] subjected conscious dogs to acute increases in balloon-induced pulmonary hypertension and classified their hemodynamic response into an "initial" phase in which cardiac output increased and a "terminal" phase in which it decreased. The observed sudden hemodynamic deterioration in our an-

TABLE II

Left Ventricular Dimensions with Increasing Pulmonary Arterial Hypertension

Mean PA Pressure (mm Hg)	L_1 EDL (mm)	L_1 Δ (mm)	L_1 %Δ	L_1 ESL (mm)	L_1 Δ (mm)	L_1 %Δ	L_2 EDL (mm)	L_2 Δ (mm)	L_2 %Δ	L_2 ESL (mm)	L_2 Δ (mm)	L_2 %Δ	L_3 EDL (mm)	L_3 Δ (mm)	L_3 %Δ	L_3 ESL (mm)	L_3 Δ (mm)	L_3 %Δ
C 13	65.9			54.2			48.2			38.4			42.5			34.3		
SE 0.8	3.1			2.9			2.9			2.7			1.9			2.2		
20	66.1	+0.2	<1	54.7	+0.5	+1	48.8	+0.6	<1	38.5	+0.1	<+1	41.2	−1.3	−3	33.4	−0.9	−3
SE 0.4	3.2	0.3		2.9	0.2		2.7	0.6		2.7	0.2		2.0	0.2		2.2	0.3	
*P<	NS			0.05			NS			NS			0.001			0.025		
30	66.0	+0.1	<1	54.4	+0.2	<+1	48.2	0	0	38.5	+0.1	<+1	39.6	−2.9	−7	32.1	−2.2	−6
SE 0.3	3.2	0.3		2.9	0.4		2.7	0.4		2.7	0.4		1.8	0.3		2.3	0.4	
P<	NS			NS			NS			NS			0.001			0.001		
40	65.7	−0.2	<−1	54.3	+0.1	<+1	47.2	−1.0	−2	37.7	−0.7	−2	37.5	−5.0	−12	30.8	−3.5	−10
SE 0.1	3.1	0.2		2.9	0.2		2.9	0.5		2.8	0.3		1.8	0.6		2.1	0.7	
P<	NS			NS			NS			NS			0.001			0.005		
50	65.0	−0.9	−1	54.8	+0.6	+1	46.3	−1.9	−4	38.3	−0.1	<−1	35.5	−7.0	−17	30.4	−3.9	−11
SE 1.2	3.0	0.3		3.0	0.5	1	3.0	0.5		2.7	0.3		1.8	0.8		1.9	0.8	
P<	0.05			NS			0.01			NS			0.001			0.005		
60	63.3	−2.6	−4	53.9	−0.3	−1	44.6	−3.6	−8	37.2	−1.2	−3	33.1	−9.4	−22	29.3	−5.0	−15
SE 0.6	3.1	0.4		3.1	0.4	1	3.3	0.7		2.7	0.6		1.8	0.8		2.0	0.6	
P<	0.001			NS			0.005			NS			0.001			0.001		

* Paired Student *t* test with control.

C = control; Δ = change from control; EDL = end-diastolic length; ESL = end-systolic length; L_1 = base-apex axis; L_2 = anterior-posterior axis; L_3 = septal-lateral axis; NS = not significant; *P* = probability; PA = pulmonary arterial; SE = standard error of the mean.

TABLE III

Mean Right Ventricular Volumes with Increasing Pulmonary Arterial Hypertension

Mean PA Pressure (mm Hg)	Dogs (no.)	Mean RVEDV (cc)	%Δ	Mean RVESV (cc)	%Δ	EF (%)
C 10	7	48		26		46
SE		5		4		4
20	7	56	+17	28	+8	50
SE		5		5		5
*P<		0.02		NS		NS
30	6	65	+35	35	+35	46
SE		6		4		2
P<		0.005		0.02		NS
40	7	70	+46	37	+42	47
SE		5		4		4
P<		0.001		0.001		NS
50	6	73	+52	38	+46	48
SE		7		5		4
P<		0.001		0.005		NS
60	4	71	+48	39	+50	45
SE		4		3		2
P<		0.005		0.02		NS

* Paired Student *t* test with control.

C = control; Δ = change from control; EF = ejection fraction; NS = not significant; *P* = probability; PA = pulmonary arterial; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; SE = standard error of the mean.

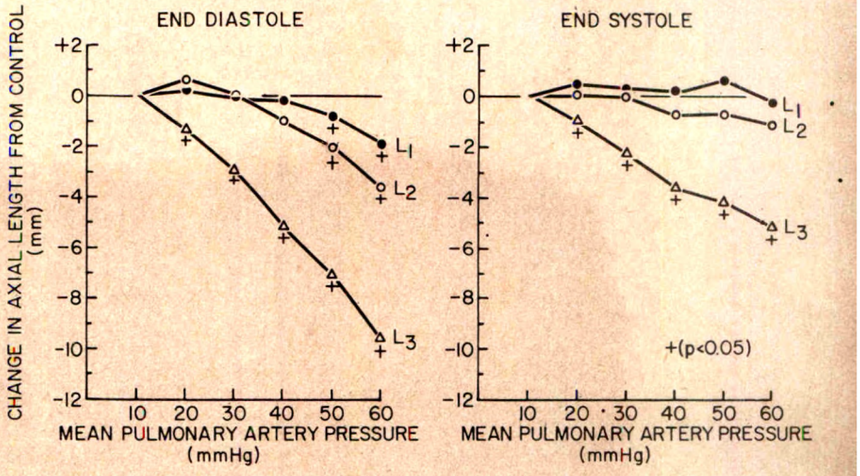

FIGURE 4. Effect of progressive pulmonary hypertension on the change in axis length from control. Positive values along the ordinate represent increase in axis length; negative values represent decrease in axis length. Each individual point represents the mean value for eight dogs, and crosses represent statistical significance to at least $P < 0.05$ (paired Student t test with respect to control value). L_1 = base-apex length; L_2 = anterior-posterior length; L_3 = septal-lateral length.

imals at a mean pulmonary arterial pressure of 60 mm Hg or more must roughly correspond to this "terminal" phase. Differences in heart rate, cardiac output and systemic vascular resistance between the two studies are probably explained by the effects of anesthetic agents or the unconscious state, or both, on autonomic tone or reflexes. The mean peak right ventricular systolic pressure of 100 mm Hg obtained in our study agrees closely with that of 95 mm Hg obtained in the study by Laks et al.,[13] and the peak right ventricular end-diastolic pressure obtained in both studies was 10 mm Hg. This finding suggests that these are the approximate maximal pressures obtainable by the dog right ventricle in response to acute pressure overload.

Ventricular Volumes

Right ventricular angiography was deferred until completion of the left ventricular dimension studies to avoid any depressant effect of contrast medium on left ventricular function.[14] The dogs were thereby subjected to prolonged experimental time, sequential reinflation of the pulmonary arterial balloon, and the possibly depressing effect of angiography itself—factors undoubtedly contributing to the inability of some of our animals to tolerate high levels of pulmonary hypertension in this latter part of the study. However, the observed increases in right ventricular end-diastolic and end-systolic volumes in response to progressive pulmonary hypertension (Table III) were qualitatively identical to those observed in a previous study from our laboratory[12] in which right ventricular biplane cineangiograms were obtained in closed chest anesthetized dogs at similar increments of balloon-induced pulmonary hypertension. In that study as in the present one, both right ventricular end-diastolic and end-systolic volumes increased approximately 50 percent from control level at a mean pulmonary arterial pressure of 60 mm Hg.

Left ventricular end-diastolic and end-systolic volumes began to decrease significantly at a mean pulmonary arterial pressure of 30 mm Hg. Neither was significantly altered at a mean pulmonary arterial pressure of 20 mm Hg. However, there was a significant (17 percent) increase in right ventricular end-diastolic volume at this mild degree of pulmonary hypertension. Left ventricular volumes markedly decreased at mean pulmonary arterial pressures of 40 to 60 mm Hg. These levels of pulmonary hypertension have previously been shown[12] to be associated with marked increases in right ventricular volume (50 percent) and with the onset of progressive tricuspid regurgitation. With the onset of tricuspid regurgitation, forward stroke volume of the right ventricle decreased.

Left Ventricular Dimensions

Analysis of the effect of acute pulmonary hypertension on left ventricular dimensions demonstrated that a characteristic distortion of left ventricular geometry accompanies the increase in right ventricular volumes. Specifically, a disproportionate shortening of the septal-lateral axis occurs at both end-diastole and end-systole at all levels of pulmonary hypertension. This is further illustrated in Figure 4, in which the mean axis data are plotted as the change in individual axis length from control values, and the statistical significance is denoted by a cross. It is obvious from this figure that at a mean pulmonary arterial pressure of 20 mm Hg the L_3 axis is significantly shortened during both end-diastole and end-systole, whereas the L_1 and L_2 axes are either unchanged or slightly (but not significantly) lengthened with respect to the control value. This selective distortion of left ventricular geometry was observed to accompany an increase in right ventricular volumes at a mild degree of pulmonary hypertension and before any significant decrease in left ventricular end-diastolic volume occurred.

In our study reductions in left ventricular end-diastolic volume were associated with an increase in heart rate. It has been shown[15,16] that increasing

heart rate characteristically causes a reduction in left ventricular end-diastolic volume. It is therefore likely that some of the observed decrease in end-diastolic volume during the progressive pulmonary hypertension was due to the associated tachycardia. The observed changes in left ventricular shape cannot be attributed to the tachycardia since studies[17] in conscious, chronically instrumented dogs indicate that tachycardia causes the left ventricle to decrease its size symmetrically.

In a recent report, Urschel et al.[18] utilized endocardial markers in an isolated dog heart preparation and observed alterations in left ventricular dimensions after volume loading to high right ventricular filling pressures while holding left ventricular stroke volume constant. The 22 percent decrease in the septal-lateral dimension during end-diastole which we observed at a mean pulmonary arterial pressure of 60 mm Hg exceeds but is directionally consistent with the 13.3 percent decrease in the septal-free wall dimension at end-diastole reported in the latter study when right ventricular end-diastolic pressure was elevated 10 mm Hg above the control level. Urschel et al.[18] found a 7 percent increase in the end-diastolic anterior-posterior dimension in a similar investigation, whereas we observed a 4 percent decrease in this dimension. This difference probably reflects the fact that a constant left ventricular stroke volume was maintained in their study by volume infusion of the left ventricle, whereas progressive right ventricular outflow obstruction led to a progressive decrease in left ventricular volume in our intact animals.

In a previous study from our laboratory, Mitchell and Mullins[7] determined the degree of systolic shortening of the L_1, L_2 and L_3 axes in more than 40 dogs previously subjected to endocardial bead placement as in this study. They found that the L_1 (base-apex) axis shortened 4 percent with each cardiac cycle, whereas the L_2 (anterior-posterior) and L_3 (septal-lateral) axes each shortened 10 percent. In our study there was a 53 percent reduction from the control value in the degree of systolic shortening of the L_3 axis at a mean pulmonary arterial pressure of 60 mm Hg compared with reductions of 25 and 20 percent for the L_2 and L_3 axes, respectively. Therefore, during each cardiac cycle at high levels of pulmonary arterial pressure there is a marked decrease in the degree of shortening of the septal-lateral axis which is out of proportion to the decrease in shortening observed in the other two axes.

Role of Septal Bulging

It is attractive to attribute this selective constriction of the left ventricular septal-lateral axis in the setting of acute pulmonary hypertension and increased right ventricular volumes to a bulging of the interventricular septum toward the cavity of the left ventricle. On right ventricular angiograms in the lateral view, the interventricular septum appears increasingly flat and less convex at increasing pulmonary arterial pressures, and this appearance also suggests encroachment on the cavity of the left ventricle.

In describing patients with isolated atrial septal defect and evidence of left ventricular decompensation, Dexter[19] suggested that bulging of the interventricular septum into the left ventricular cavity secondary to a markedly distended right ventricle may play an etiologic role. He coined the term "reversed Bernheim effect," likening this phenomenon to that described by Bernheim, in which right ventricular outflow was obstructed by septal hypertrophy and contributed to inordinate right ventricular failure in patients with pure left ventricular obstructive lesions.[20] Another explanation of our findings is that distortion of the septal fibers of the left ventricle caused by dilatation of the right ventricle might cause the change in the septal-lateral axis.

Our investigation clearly shows a selective change in left ventricular geometry resulting from right ventricular pressure overload in the closed chest dog. The distortion in geometry of the left ventricle shown by dimensional studies may contribute significantly to the apparent decrease in left ventricular compliance observed in volume-loaded animal preparations subjected to right ventricular pressure overload. Perhaps the clinical counterpart of this finding is seen in unexplained increases in left ventricular filling pressure observed in conjunction with primary right ventricular overload states in man.

Acknowledgment

We gratefully acknowledge the technical help of Harold Alsobrook, James Jones, Delories LaRue, and Nelda Holcombe, and the secretarial support of Pat Wells and Elizabeth Schutz.

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Ventricular Conduction Delay and Asystole During Systemic Hyperkalemia

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Systemic hyperkalemia was induced in 30 intact dogs to evaluate electrophysiologic and hemodynamic alterations caused by excess of potassium (K^+) ion. Sequential changes included atrioventricular junctional delay and block, followed by acceleration of junctional pacemakers and conduction delays in the ventricular specialized tissue and ventricular muscle. These resulted in unusual arrhythmias difficult to interpret in the peripheral electrocardiogram. As the level of potassium progressively rose, terminal Purkinje or Purkinje-muscle block was the dominant mechanism of arrest, with conduction through the ventricular specialized conduction system continuing at a regular rate even after asystole. The duration and amplitude of the intramural complexes were consistently reduced throughout the heart wall, whereas intramural conduction was progressively prolonged with late and inconstant changes in activation sequence. Ventricular pacing thresholds increased progressively, but were attainable even after asystole in some cases. The enhanced plasma K^+ was associated with accumulation of K^+ and sodium (Na^+) in myocardial tissue. A relatively uniform distribution of these ions from endocardium to epicardium is postulated to be a requirement for progressive conduction delay, lack of ectopic beats and asystole. Systemic arterial pressure and coronary blood flow were maintained until very high levels of K^+ were reached. Although left ventricular end-diastolic pressure increased progressively, the maximal rate of rise of left ventricular pressure (dP/dt max) was reduced only at a K^+ level of 11 mEq/liter. Myocardial ischemia was not present, thus suggesting that the abnormal ventricular function may have been secondary to conduction delays.

Increased extracellular potassium ion (K^+) and hypoxia similarly alter the action potential of isolated cardiac muscle.[1–3] However, the nodal, Purkinje and heart muscle cells have different sensitivities to acutely increased extracellular K^+.[3] This study was designed to determine the relation of conduction delay in the fascicular system of the left ventricle to intramural conduction during a period of gradual plasma potassium increments. Determination of the relative degree of depressed impulse conduction in the different segments of the conduction system not only may clarify the mechanism of asystole but also may, by contrast, facilitate understanding of the conditions underlying arrhythmogenesis during local intracoronary K^+ infusion.[4] In addition, the relative uniformity of altered myocardial cation composition has been assessed, as well as myocardial function and the response of the coronary circulation during hyperkalemia.

Methods

Healthy male mongrel dogs of similar ages, weighing 19 to 35 kg, were studied. In all animals, premedication was effected with morphine sulfate, 3 mg/kg, and anesthesia was induced with 12 mg/kg of intravenously adminis-

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tered sodium pentobarbital. After endotracheal intubation and placement of the animal in a left lateral position, respirations were maintained with a mechanical respirator. Surgical incisions exposed jugular, carotid, axillary and femoral vessels for catheterization. Several aspects of hyperkalemia were evaluated, including specialized fiber activation, transmural electrographic changes, alterations of ventricular function and coronary blood flow and changes in ventricular pacing threshold and myocardial ion distributions. Each animal was included in at least one phase of these investigations.

To monitor hemodynamics, a saline-filled no. 8F Goodale-Lubin catheter was placed, under fluoroscopic control, in the left ventricle from the axilla and connected to a Statham P23Gb pressure gauge, the electrical output of which was displayed and recorded on an Electronics for Medicine DR-8 photographic recorder. The first derivative of left ventricular pressure rise (dP/dt) was obtained by resistance-capacitance differentiation of the pressure pulse. Another no. 8F Goodale-Lubin catheter was advanced by way of a jugular vein into the mid to high coronary sinus and connected to tubing used for infusion of saline solution. A femoral vein was used for infusion.

For specialized fiber recording, an electrode catheter of the tri-polar Castillo type (Electro-Catheter Corp., Rahway, N. J.) was thermally preshaped in hot water by curving the distal 7 cm into a "J," then passed through a carotid artery into the region of the right coronary cusp of the aortic valve. From this location it is possible to record a His bundle electrogram.[5–7] Recordings with the distal (close bipolar) pair were made utilizing a multiple electrode switch box (Electronics for Medicine), the output of which was led into the alternating current input of an electrocardiographic preamplifier and recorded on photographic paper at a speed of 200 mm/sec. A second similar electrode catheter was advanced through the other carotid artery into the left ventricle and directed anteriorly to record from a branch of the peripheral Purkinje radiation of the left bundle branch (or anterior false tendon). Impulses were filtered at 40 to 500 cycles/sec. Recording from the bundle branch has been similarly demonstrated by this technique in the dog[5,6] and in man.[7,8] The bipolar electrogram from this site was recorded simultaneously with the His bundle electrogram and a peripheral electrocardiographic lead, usually lead II. To ensure that a portion of the QRS complex was not isoelectric in that lead, the other two standard leads were also recorded with the electrograms. Early in the study, several animals underwent pacing from the right atrium at rates 5 to 10 beats/min in excess of sinus rate to maintain rate constancy, but this procedure was abandoned because of the early development of block at the atrioventricular (A–V) junction.

H–Q (or H–V, the interval from the first rapid deflection of the His bundle complex to the onset of the QRS complex), H–a (the interval from the His bundle to the false tendon complex) and QRS duration were all measured by hand in three representative beats at each measurement period and the means recorded to the nearest 0.2 msec.

Coronary blood flow was determined at rest and during induced hyperkalemia by retrograde injection of a solution of krypton-85 into the coronary sinus and observing the subsequent washout with a precordial scintillation counter.[9] Coronary blood flow (CBF) was calculated by the relation $CBF = (0.693 \times 100)/t_{1/2}$, where $t_{1/2}$ is the time in minutes required for decline of radioactivity to half of its value.

For implantation of transmural electrodes, a left thoracotomy and pericardiotomy were performed after anesthesia, and the heart was suspended in a pericardial cradle. Bipolar electrodes[10,11] made of Teflon®-coated stainless steel wire formed into small hooks (diameter 0.007 inch, Medwire Corp., Mt. Vernon, N. Y.) were placed through hypodermic needles into the endocardium and epicardium of

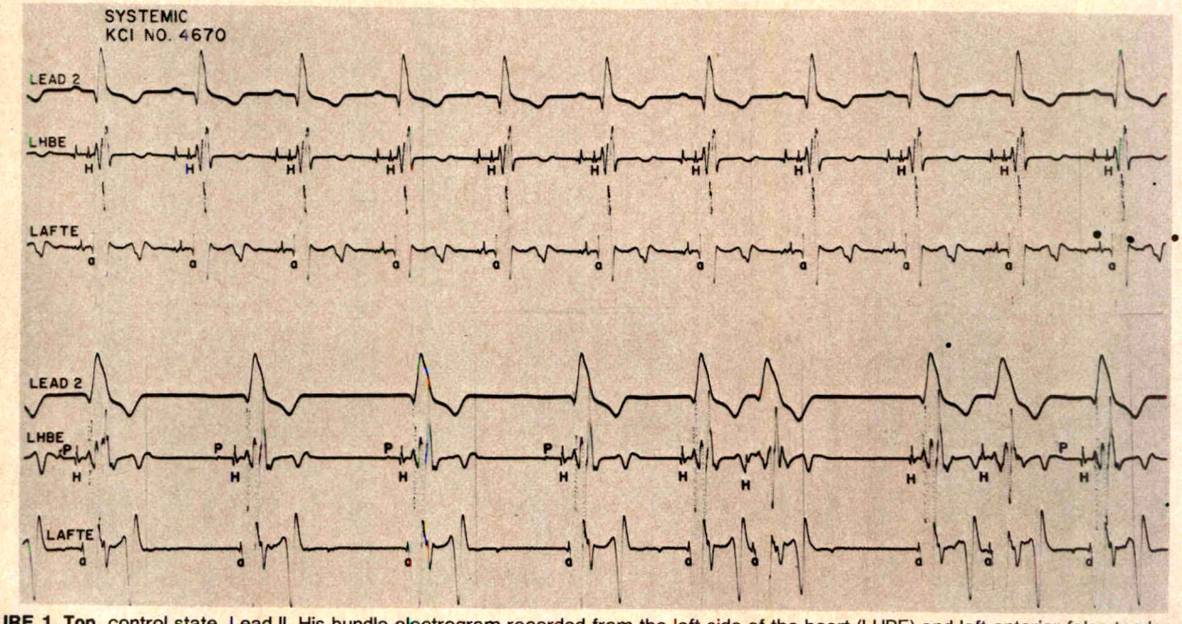

FIGURE 1. Top, control state. Lead II, His bundle electrogram recorded from the left side of the heart (LHBE) and left anterior false tendon electrogram (LAFTE). His (H) and bundle branch (a) impulses precede each QRS. **Bottom,** during hyperkalemia. The QRS complex is wider and slurred, although its configuration has not changed. P waves are absent from the peripheral electrocardiogram but are seen in LHBE to precede the first four beats. The fifth beat probably is of junctional origin (no P wave); all beats, however, are preceded by H and a impulses although these are slurred with the H–Q and H–a intervals prolonged. In this and all succeeding electrograms, paper speed = 200 mm/sec, time lines 1/sec except as otherwise noted.

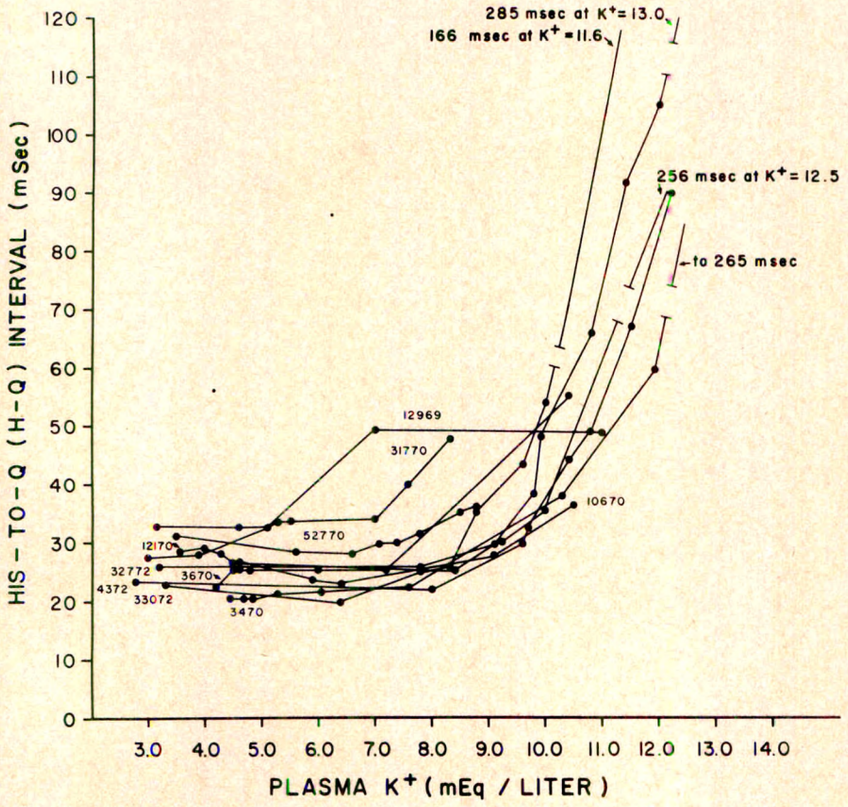

FIGURE 2. His–Q interval as a function of increasing plasma K^+. Major increases in the His–Q interval occur after a K^+ level of 9 to 10 mEq/liter. Several animals showed a transient shortening of the His–Q interval as K^+ increased in the range of 5 to 8 mEq/liter. (Numbers identify individual animals.)

TABLE I

Summary of Intramural Electrophysiologic Data in Five Animals

	Control	Moderate Hyperkalemia*	Severe Hyperkalemia*
QRS duration (msec)	53 ± 3	75 ± 8†	161 ± 42‡
Q–T_c of QRS (msec)	332 ± 15	337 ± 15	375 ± 54
Electrographic voltage (% of control)			
Endocardial	100	55 ± 9‡	41 ± 8‡
Epicardial	100	69 ± 5‡	42 ± 10‡
Electrogram Q–T_c (msec)			
Endocardial	313 ± 11	300 ± 10§	263 ± 21§
Epicardial	308 ± 11	279 ± 11‡	256 ± 25§
Transmural (endocardial-epicardial) conduction time (msec)	17 ± 0	21 ± 2§	42 ± 8§

* Moderate hyperkalemia was at $K^+ \sim 8$ to 10.5 mEq/liter; severe hyperkalemia was the last recording before asystole, at $K^+ \sim 11$ to 15 mEq/liter.

† $P < 0.01$ compared with control; ‡ $P < 0.001$ compared with control; § $P < 0.005$ compared with control.

Since K^+ is known to reduce action potential height and duration and to prolong conduction and was assumed to alter local electrograms similarly, a one-tailed t test was used in these statistical calculations. Changes in voltage, Q–T_c interval and conduction time occurred in the same direction in all animals.

the left ventricular free wall midway between the apex and the base. These electrode pairs were 1 to 2 mm apart after placement, with individual diameters of 0.005 inch. The endocardial and epicardial electrodes were placed radially in relation to each other, that is, along an imaginary line traversing the free wall perpendicularly. These bipolar wire pairs were led through the multiple electrode switch box; intramural electrograms were filtered at 0.1 to 2,000 cycles/sec and recorded at 200 mm/sec; the first derivative of rise in voltage (dV/dt) of each was also obtained by resistance-capacitance differentiation. After satisfactory electrode placement, as evidenced by recording of a single sharp deflection sometimes followed by S–T segment displacement, the chest was closed and the animal allowed to rest until the S–T injury disappeared from the electrograms, a period of approximately 1 hour.

After recording of the endocardial and epicardial electrograms, the absolute height of the electrographic spike was measured at each stage of infusion and expressed as percent of control. The individual Q–T_c duration at both myocardial levels was calculated as Q–T_c = observed Q–T/$\sqrt{\text{R–R}}$ interval. The time between the peaks of the endocardial and epicardial complexes was measured as the transmural conduction time. DV/dt max was recorded intermittently and expressed as a percent of the control level of dV/dt max.

Bipolar epicardial and endocardial pacing thresholds were subsequently determined at rest and during hyperkalemia through these intramural electrodes with a Medtronic model 5737 pacemaker, calibrated to deliver impulses of known strength. In several animals, with use of the syn-

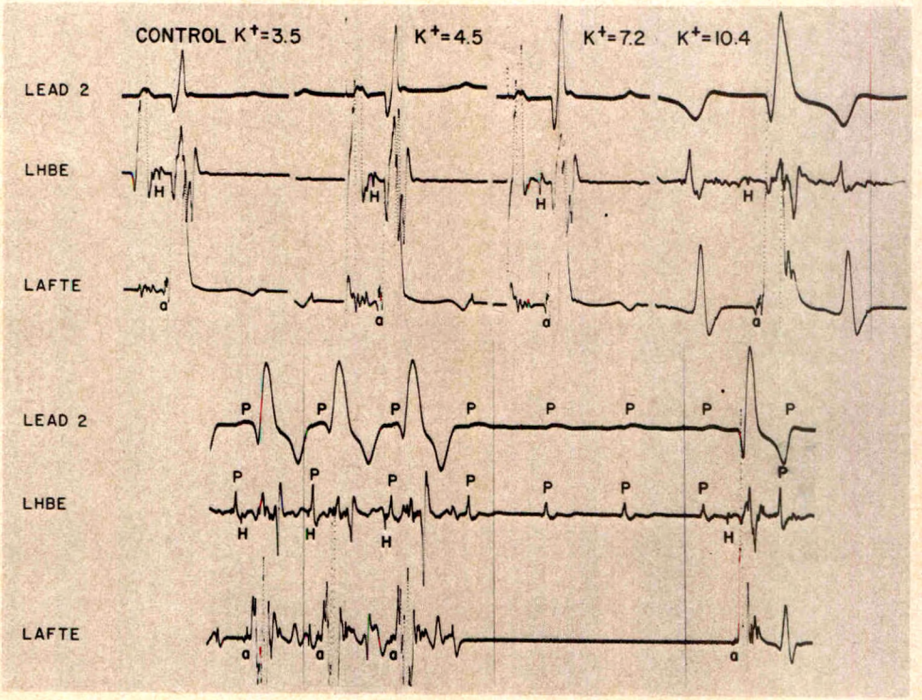

FIGURE 3. Top, rapid increase in QRS duration and H–Q interval as plasma K^+ increases across a critical range from 7.2 to 10.4 mEq/liter. His bundle (H) and anterior false tendon (a) impulses precede each QRS complex. The P–R segment lengthens progressively and the P wave diminishes in amplitude. **Bottom,** at K^+ level of 10.4 mEq/liter. Dissociation between the P and H complexes is now present. QRS complexes occur irregularly but each is preceded by H and a impulses. A–V junctional block is present and the ventricles are activated by an irregular, accelerated junctional mechanism. The last QRS complex may be conducted from the preceding P wave.

chronizing mode of the pacemaker, a ventricular stimulus impulse of twice diastolic threshold was gradually allowed to approach the T wave of the previous normal beat until it failed to produce an extrasystole, in an effort to induce a repetitive ventricular response.[12]

In all animals blood hematocrit and pH were normal in the control state. Duplicate samples of arterial and coronary sinus blood were drawn, pressures or electrical events, or both, measured, and an infusion of isotonic potassium chloride into the inferior vena cava was begun at rates of 12 or 24 cc (1.7 or 3.4 mEq)/min, depending upon the size of the animal. Blood drawn was replaced in equivalent amount from a donor animal. Electrical activity and hemodynamic variables were recorded and blood samples taken at increments of 4 to 8 minutes at first, and later at shorter intervals. These measurements and coronary blood flow determinations were subsequently correlated with plasma K^+ levels.

Studies were terminated by the development of asystole (28 animals) or ventricular fibrillation (2 animals). The hearts were quickly removed by thoracotomy (30 seconds) and placed in iced Ringers solution. Full thickness segments of free left ventricular wall from the left anterior descending and circumflex coronary arterial regions were removed and rapidly divided by sharp dissection into inner, middle and outer thirds and then frozen in liquid nitrogen and freezer-stored for subsequent analysis of water, K^+ and Na^+ [13] content. Tissue water was determined by weight difference before and after oven drying of a tissue homogenate overnight at 110° C.

Statistical analyses were performed by computer using standard techniques for small samples. Means were compared using Student's *t* test, unpaired when evaluating tissue changes in hyperkalemic and normal animals and paired when comparing electrical changes in the hyperkalemic animals.

Results

Electrophysiologic changes: As noted by prior investigators,[14,15] hyperkalemia initially became manifest by peaking of T waves and shortening of the $Q–T_c$ interval. Heart rate tended to slow during infusion, although this was somewhat variable in different animals. P waves became reduced in amplitude until they could not be seen in the peripheral electrocardiogram at K^+ levels of 8 to 10 mEq/liter; at these levels the ventricular response generally became irregular, at times with Wenckebach periodicity, but invariably with His bundle and bundle branch impulses preceding each QRS complex (Fig. 1).

His–Q and QRS durations increased rapidly at higher levels of K^+ (Fig. 2, Table I). In several animals the His–Q interval shortened by 10 to 15 percent at K^+ levels of 5 to 7 mEq/liter or more; this change was not accompanied by a measurable change in the QRS complex. His–Q and QRS durations remained relatively stable until levels of K^+ greater than 8 to 9 mEq/liter were reached, after which both increased rapidly. The His complex itself became wider, more slurred and of lower amplitude. The QRS complex became first widened, then distorted as hyperkalemia progressed (Fig. 3). In addition, block at the A–V nodal level frequently became evident at K^+ levels of ≥10 mEq/liter, with dissociation of atrial and ventricular complexes, the latter always preceded by His and bundle branch impulses.

Increases observed in the H–Q and in H–a intervals were of similar degree initially, but block distal to the bundle branch recording site became evident

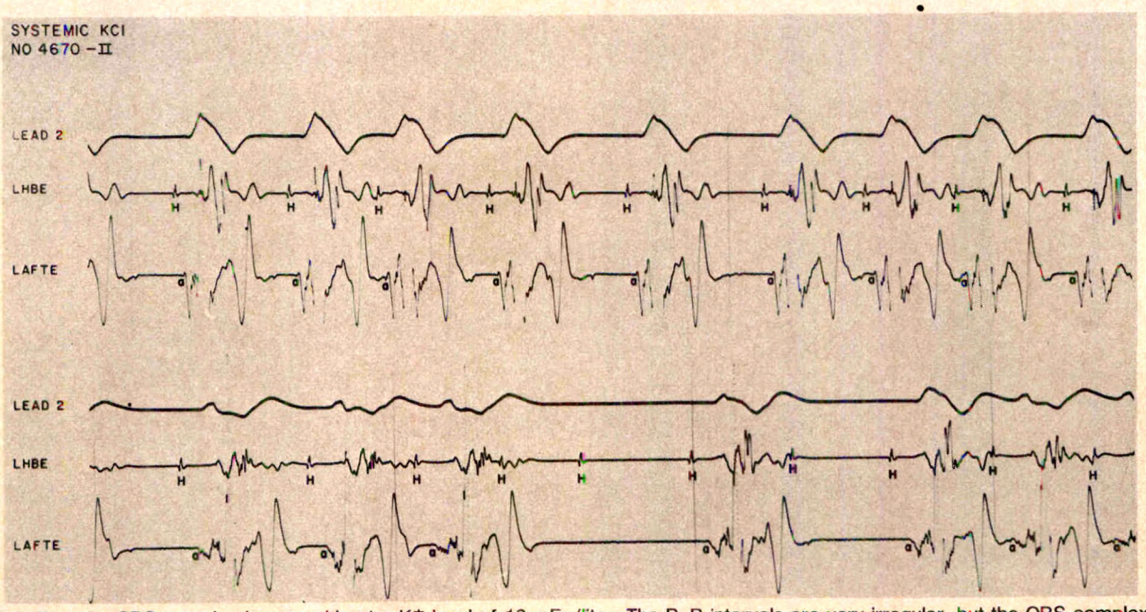

FIGURE 4. Top, the QRS complex is very wide at a K^+ level of 12 mEq/liter. The R–R intervals are very irregular, but the QRS complex is obviously of supraventricular origin since an H deflection precedes each. Bundle branch impulses are present but poorly seen because of slowing and reduction of amplitude. **Bottom,** slightly later. Gross distortion of the QRS complex is seen. The first five (H) impulses occur progressively earlier, suggesting a possible Wenckebach phenomenon, but the subsequent H impulses are not regular enough to verify this possibility. Block within the His-Purkinje system is demonstrated by failure of the fourth, fifth and seventh His impulses to be conducted to the ventricles. Bundle branch impulses are not well seen.

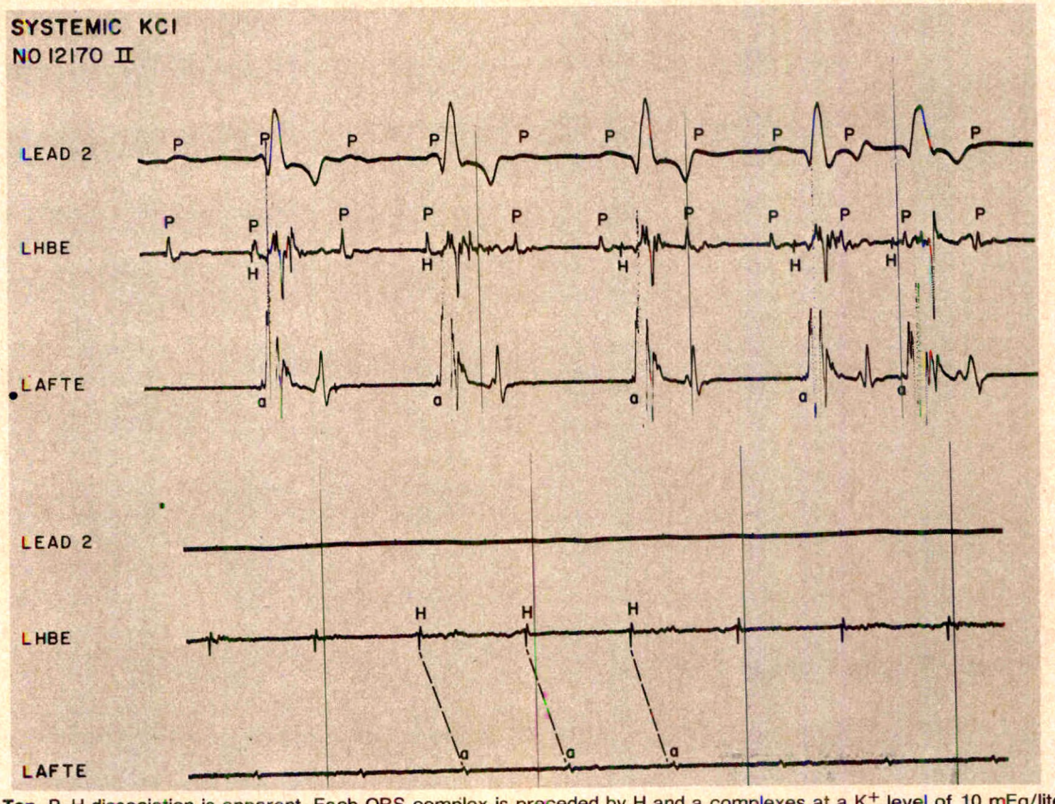

FIGURE 5. Top, P–H dissociation is apparent. Each QRS complex is preceded by H and a complexes at a K^+ level of 10 mEq/liter. **Bottom,** 1 minute later, asystole is seen on the peripheral electrocardiogram although H impulses continue to be generated and regularly conducted to (or possibly through) the bundle branch recording site. This technique cannot distinguish between block in the distal Purkinje system or at the Purkinje-muscle junction. Paper speed = 100 mm/sec in both panels.

TABLE II

Hemodynamics During Systemic Hyperkalemia (means ± standard error)

Variable	K^+ (mEq/liter)					
	Control (<5.0) (mean 3.5 ± 0.2)	5.1–7.0 (mean 6.4 ± 0.2)	7.1–9.0 (mean 8.1 ± 0.2)	9.1–11.0 (mean 9.9 ± 0.1)	11.1–13.0 (mean 12.1 ± 0.2)	>13.1 (mean 13.9 ± 0.3)
LV pressure (mm Hg)						
Systolic						
Mean	132	136	149	129	128	103
SE	10	8	5	5	11	37
no.*	10	6	16	17	10	2
Diastolic						
Mean	6	9	11†	14‡	22§	19
SE	1	2	2	2	4	2
no.	10	6	16	17	10	2
LV dP/dt max (mm Hg/sec)						
Mean	2506	2282	2478	1974	1358‡	840
SE	277	99	118	142	181	315
no.	10	6	16	17	10	2
Coronary blood flow (ml/100 g per min)						
Mean	97	122	124	115	128	...
SE	11	19	20	14	28	...
no.	8	7	8	8	3¶	...
Heart rate (beats/min)						
Mean	143	165	137	105	66	112
SE	18	22	10	7	9	24
no.	8	5	14	15	9	2

* Values obtained in 10 animals; no. = number of observation at each K^+ level.
† $P<0.05$ compared with control; ‡ $P<0.01$ compared with control; § $P<0.001$ compared with control.
¶ Includes all flows at a K^+ value of 11 mEq/liter.

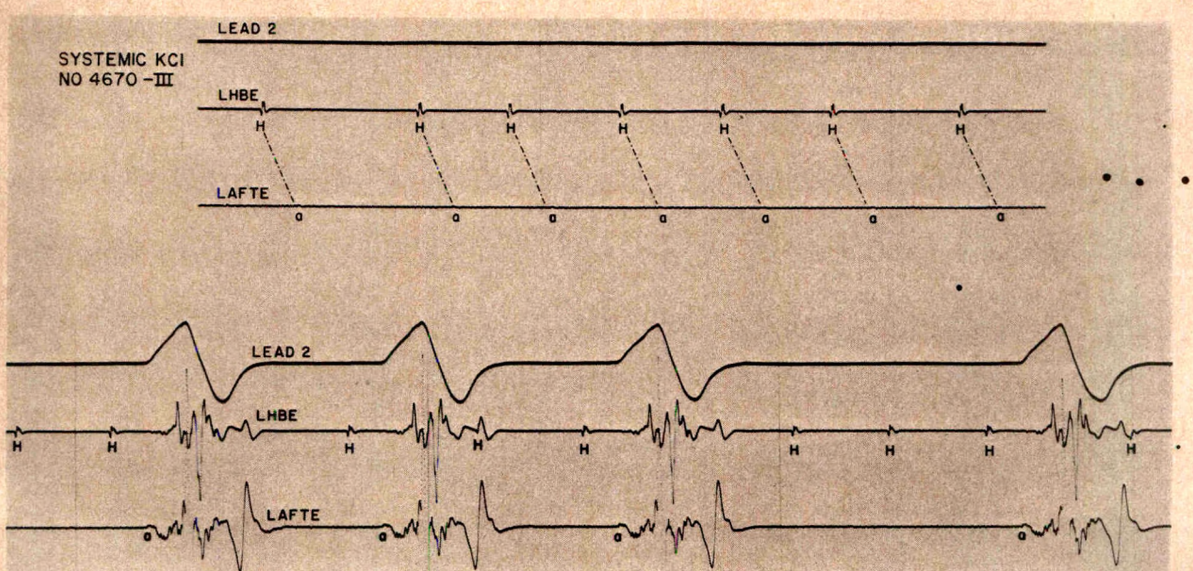

FIGURE 6. Top, at asystole. Conduction impulses continue to be irregularly generated and transmitted from the His bundle to the bundle branches. **Bottom,** a few seconds later. The QRS complex reappears, greatly widened, despite continuation of infusion. Since each QRS complex is preceded by an H complex at a constant interval, it is conducted from above, probably from the A–V junctional region. Further slurring of the H and QRS complexes is evident.

in several animals at K^+ levels of 10 to 12 mEq/liter, when the ventricular rhythm became more regular, with very wide, slurred QRS complexes, and each QRS complex was at first preceded by a delayed and slurred His complex and a bundle branch complex. Some unusual sequences then developed (Fig. 4), indicating block below the His bundle in the distal conduction system. Asystole sometimes developed suddenly as a result of terminal Purkinje or Purkinje-muscle block (Fig. 5 and 6). Although peripheral electrocardiographic activity ceased, impulses traveling from the His bundle to a bundle branch were demonstrated. The terminal rhythm was asystole in 28 or 30 animals; 2 animals died suddenly with ventricular fibrillation.

A rapid rhythm with a wide QRS complex began suddenly in two experiments at very high levels of K^+ (Fig. 7). Although this rhythm was apparently ventricular tachycardia, widening and fusion of the QRS–T complexes prevented accurate assessment of the rhythm by the His bundle technique. This rhythm resembled that described by Vassalle et al.[16] and Cohen at al.[17] as ventricular flutter.

At terminus, the mean arterial and coronary sinus plasma K^+ levels were 12.4 and 11.5 mEq/liter, respectively. This difference was not statistically significant.

Hemodynamic changes: Left ventricular systolic pressures remained unchanged until plasma K^+ reached levels inducing asystole (Table II). Left ventricular end-diastolic pressure increased consistently in every animal even with modest increases in K^+. Since ventricular volume was not measured, it is uncertain whether this increase was due primarily to diminished ventricular function or to increased preload and/or reduced compliance, or both. Left ventricular dP/dt max decreased significantly at a K^+ level greater than 11 mEq/liter. Mean coronary blood flow did not change significantly in six animals studied; ischemia was not present in any experiment.

Intramural electrocardiographic changes: As hyperkalemia progressed, the absolute height and rate of rise (dV/dt max) of the intramural electrograms decreased (Fig. 8). The time from endocardial to epicardial activation progressively increased as well, all indicating slowed conduction through the ventricular wall. Table I summarizes the intramural electrophysiologic changes during hyperkalemia. As the QRS complex increased, the $Q–T_c$ component of the QRS complex did not change significantly, indicating a net shortening of $Q–T_c$ relative to the QRS complex (decline in $|Q\text{-}T_c–QRS|$). Voltage reduction to approximately 41 percent of the control level occurred in both endocardium and epicardium, with a

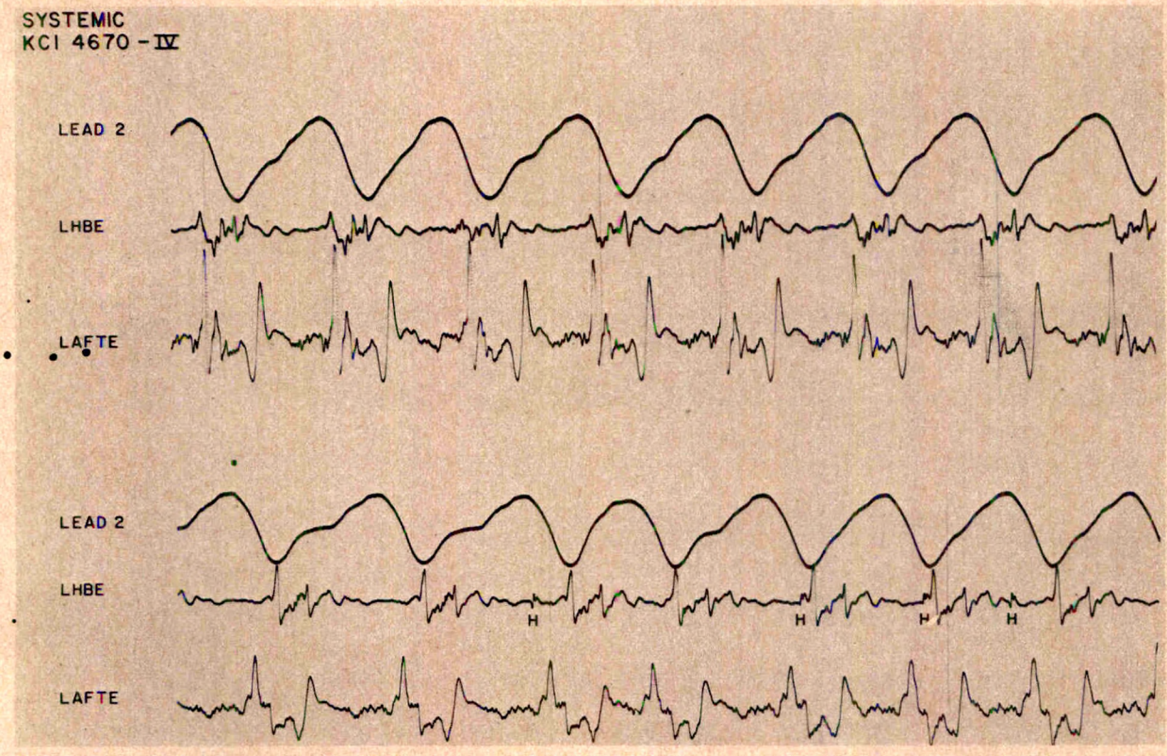

FIGURE 7. Top, the rapid, regular and wide QRS complex suggests ventricular tachycardia. Continuous electrical activity defies analysis by the electrode catheter technique. **Bottom,** a more irregular section uncovers apparent H complexes, but the irregularly appearing His activation bears no obvious relation to the QRS complex. Ventricular tachycardia remains the most likely possibility. This rhythm was rarely seen, and only at a K^+ level greater than 10 mEq/liter.

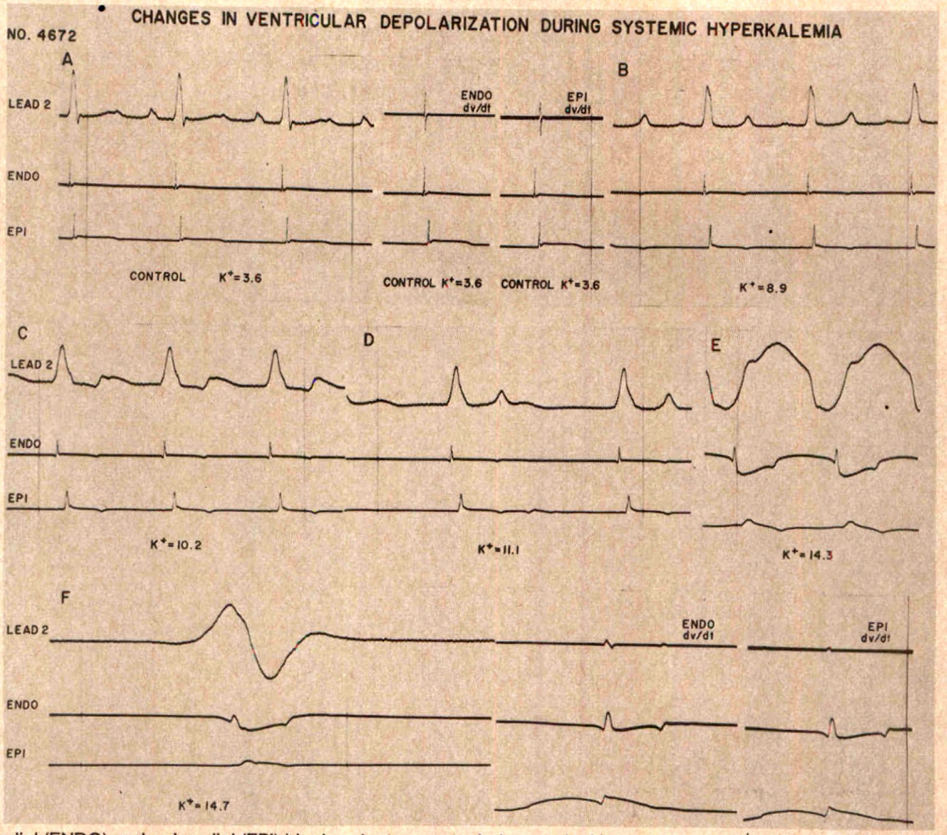

FIGURE 8. Endocardial (ENDO) and epicardial (EPI) bipolar electrograms during gradual hyperkalemia. K^+ concentration during each recording is indicated. Electrographic spike height and maximal rate of rise (dV/dt) progressively decline until pronounced slurring is evident **(E, F).** Endocardial and epicardial sites are affected to a similar degree and the Q–T interval at each location is also similar, correlating with the homogeneous increments of tissue K^+ observed in outer and inner wall layers. From the time electrograms were recorded in **F** to the time dV/dt values were recorded, the temporal relation between endo- and epicardial activation changed, implying a late change in activation sequence.

similar shortening of electrographic Q–T_c interval by approximately 15 percent in each. Transmural conduction time increased by 150 percent. DV/dt max was measured in three animals and declined in all to a similar degree in outer and inner layers.

Altered ventricular excitability was determined by endocardial and epicardial pacing thresholds during hyperkalemia (Fig. 9). Pacing thresholds remained constant until the K^+ level was 9 mEq/liter, after which they increased rapidly. After conduction block had induced asystole, ventricular pacing in several animals maintained cardiac contraction.

Early premature ventricular beats were induced to evaluate the possibility that conduction slowing might allow reentry to occur or that increased excitability would be "unmasked." Neither phenomenon was observed.

Myocardial water and electrolyte content: Values for left ventricular tissue water (percent of wet weight), K^+ and Na^+ (μEq/g wet weight) were determined in 21 hyperkalemic dogs at asystole and compared with values in 6 normal dogs studied in this laboratory (Table III). Data presented are from the outer, middle and inner thirds of a full thickness segment from the region of the left anterior descending coronary artery. The circumflex arterial area was also analyzed in 8 dogs and was of similar composition. Tissue water was unchanged. Myocardial electrolyte determination reflected a homogeneous increment of K^+ throughout the left ventricular wall, and myocardial Na^+ was similarly increased. These uniform increases paralleled the similar endocardial and epicardial electrical changes observed with the intramural leads.

Discussion

Hyperkalemia occurs in renal failure and may induce serious cardiac rhythm disturbances in this clinical setting. Yet potassium ion has been utilized for its antiarrhythmic properties,[18–27] although potentiation of digitalis-induced A–V block[28] and A–V block induced by increased extracellular K^+ alone at high concentrations[29] or during rapidly increasing extracellular K^+ levels in hypokalemia[14,30,31] may occur with hazard.[32–34] Hyperkalemic cardiac arrest was first observed experimentally by Hering in 1907.[35]

Conduction changes during hyperkalemia: Increased extracellular K^+ lowers myocardial resting membrane potential and shortens the action potential.[3,36] The latter induces Q–T_c shortening, which

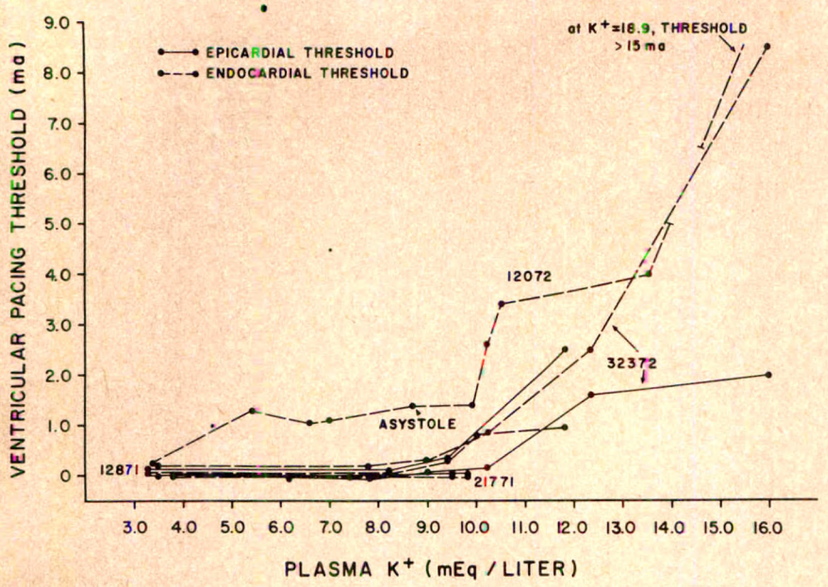

FIGURE 9. Epicardial and endocardial pacing thresholds during progressive hyperkalemia. Increases in threshold appeared similarly in both layers at a K^+ level of 9 to 10 mEq/liter and were continuous. Two animals underwent pacing for several minutes after spontaneous asystole had occurred (data in one are shown here). Asystole occurs because of failure of propagation of activation in the His-Purkinje system; the cardiac muscle is capable of continued contraction if sufficient electrical stimulus is applied.

was apparent after onset of infusion in our animals as in the study of Surawicz et al.[14] The Q–T_c interval prolonged only after the QRS complex had greatly widened. Despite QRS prolongation, it was apparent from our bipolar electrographic studies (Table I, Fig. 8) that local action potentials remained shortened even during severe hyperkalemia, thus indicating that QRS prolongation is a direct result of severe intraventricular conduction delay. Indeed, when the asystolic heart was removed from the hyperkalemic animal, slow rhythmic contractile waves began to traverse the ventricular surfaces in constant motion. The simultaneous presence of depolarization and repolarization processes during hyperkalemia was noted previously by Vassalle et al.[16]

We measured ventricular excitability by determination of endocardial and epicardial pacing thresholds during hyperkalemia. Several previous investigations have indicated a transient decrease in diastolic threshold at slightly elevated levels of K^+,[37–39] but another study[40] as well as our own failed to confirm this decline. Since depression of conduction may also account for changes in pacing threshold, the increased threshold observed at a K^+ level higher than 10 mEq/liter by ourselves and others may have been due in part to failure of local depolarization impulses to propagate.

The sequence of conduction changes as K^+ increased was usually reproducible. Flattening and disappearance of P waves occurred early. Disappearance of the P wave from the peripheral electrocardiogram does not imply loss of sinus activation[16] but is attributed to the differential effects of hyperkalemia upon atrial muscle and atrial conducting fibers.[41–43] After disappearance of the P wave, R–R intervals frequently became irregular. Sometimes typical Wenckebach periodicity of the QRS complex indicated progressive A–V nodal block (the H–Q interval was unchanged during the Wenckebach episode). Cohen et al.[17] demonstrated that loss of atrial conduction to the ventri-

TABLE III

Myocardial Water and Electrolyte Content (means ± standard error)

	% Water			K^+ (μEq/g wet weight)			Na^+ (μEq/g wet weight)		
	Epi	Mid	Endo	Epi	Mid	Endo	Epi	Mid	Endo
Hyperkalemic									
(no. = 21)	78.7†	79.2	79.6	81.3	78.1	77.9	36.3	36.0	39.8
	0.5	0.7	0.8	2.7	2.5	2.8	2.1	1.8	2.2
*P**	NS	NS	NS	<0.001	<0.001	<0.005	<0.1	<0.05	<0.025
Normal									
(no. = 6)	79.1	79.6	79.6	61.6	60.8	60.7	28.7	28.6	29.8
	0.5	0.6	0.4	1.0	1.1	1.1	1.7	1.2	1.7

* *P* value compares hyperkalemic and normal animals for the same layer.

Epi, Mid and Endo refer to outer, middle and inner thirds of a transmural segment from the region of the left anterior descending coronary artery; NS = not significant; *P* = probability.

cles occurred commonly during hyperkalemia. In their view, a junctional pacemaker was likely to be the origin of conducted beats at higher levels of K^+ since excess K^+ in man slows the primary pacemaker and accelerates subsidiary centers.[44] Atrial complexes recorded in several of our dogs showed dissociation between the atrial and the His bundle depolarizations, thus supporting this view (Fig. 3 and 5).

Asystole in hyperkalemia: The form of the QRS complex was at first similar to that of the control complex, thus indicating similar depolarization sequences. However, at K^+ levels greater than 10 mEq/liter, the QRS configuration usually changed suddenly when moderately widened, and local changes in the depolarization sequence within the myocardium were regularly observed near asystole (Fig. 8). Asystole was often associated with continued passage of conduction impulses down the Purkinje network. Mendez et al.[45] demonstrated in isolated canine Purkinje fiber-papillary muscle preparations that moderate increases of extracellular K^+ decreased conduction delay at this junction whereas higher concentrations increased it, and at K^+ levels of 10 to 11 mmoles/liter, total conduction block occurred. In our dogs, terminal Purkinje-muscle block may have occurred at slightly different times in different areas as plasma and tissue K^+ levels rose, thus accounting for the late morphologic changes in the QRS complex (changes in depolarization sequence) and, finally, asystole. The lesser sensitivity of ventricular Purkinje tissue to hyperkalemia compared with that of ventricular muscle was again demonstrated.

Myocardial contractility: Although increased extracellular K^+ reportedly diminished myocardial contractility in the isolated heart[46,47] as compared with the intact animal,[31,48,49] left ventricular dP/dt max at constant afterload (left ventricular systolic pressure did not fall) declined only at K^+ levels of more than 11 mEq/liter in our investigation. Left ventricular end-diastolic pressure increased progressively, contrary to the findings of Surawicz.[14] Failure of contractility to decrease until conduction alterations were pronounced suggested that the declining contractility at high K^+ levels may have been a result of the conduction changes that were occurring simultaneously.

Myocardial uptake and distribution of K^+: Myocardial K^+ uptake was uniform in different regions and transmurally, as demonstrated by tissue analysis, and similar homogeneous effects upon conduction were expected. As Table I indicates, reduction of action potential amplitude and duration (electrographic height and Q–T interval) were similar in inner and outer myocardial layers, contrasting with the heterogeneous electrical and ionic alterations observed during local intracoronary K^+ perfusion experiments in our laboratory, in which K^+ effects were significantly greater in epicardium than in endocardium.[4]

Localized cardiac hyperkalemia[4,50–54] results in S–T segment elevation and ventricular arrhythmias, the latter probably of reentrant origin.[4] S–T segment elevation was never observed in our experiments during systemic K^+ infusion, and ventricular extrasystoles were distinctly unusual. These findings suggest that homogeneity of conduction slowing eventuates in asystole and, conversely, that nonuniform conduction slowing tends to induce arrhythmias. Rapid systemic administration of a bolus injection of K^+ induces ventricular fibrillation as well as transient conduction disturbances, possibly because of initial lack of uniform distribution of this ion as it arrives in the heart.

Clinical implications: Since potassium rapidly depresses conduction at plasma levels in excess of 9 to 10 mEq/liter, minor reductions in K^+ by such expedients as glucose-insulin infusions may quickly restore conduction. Potassium salts may exert their antiarrhythmic effects by transient acceleration of conduction during modest hyperkalemia or by slowing of conduction at higher levels, either of which may interrupt a reentrant pathway. However, control of dosage is difficult and therapy hazardous when major conduction changes occur within such a narrow range of concentrations.

Acknowledgment

The technical assistance of Mrs. B. Jenkins, Mrs. L. Djeu, Miss R. Manno and Mrs. F. Herdman and the secretarial services rendered by Mrs. A. Binetti and Mrs. A. Brown are gratefully acknowledged. Intramyocardial electrode wires and technical advice were provided by Dr. B. Scherlag, Mt. Sinai Hospital, Miami Beach, Fla.

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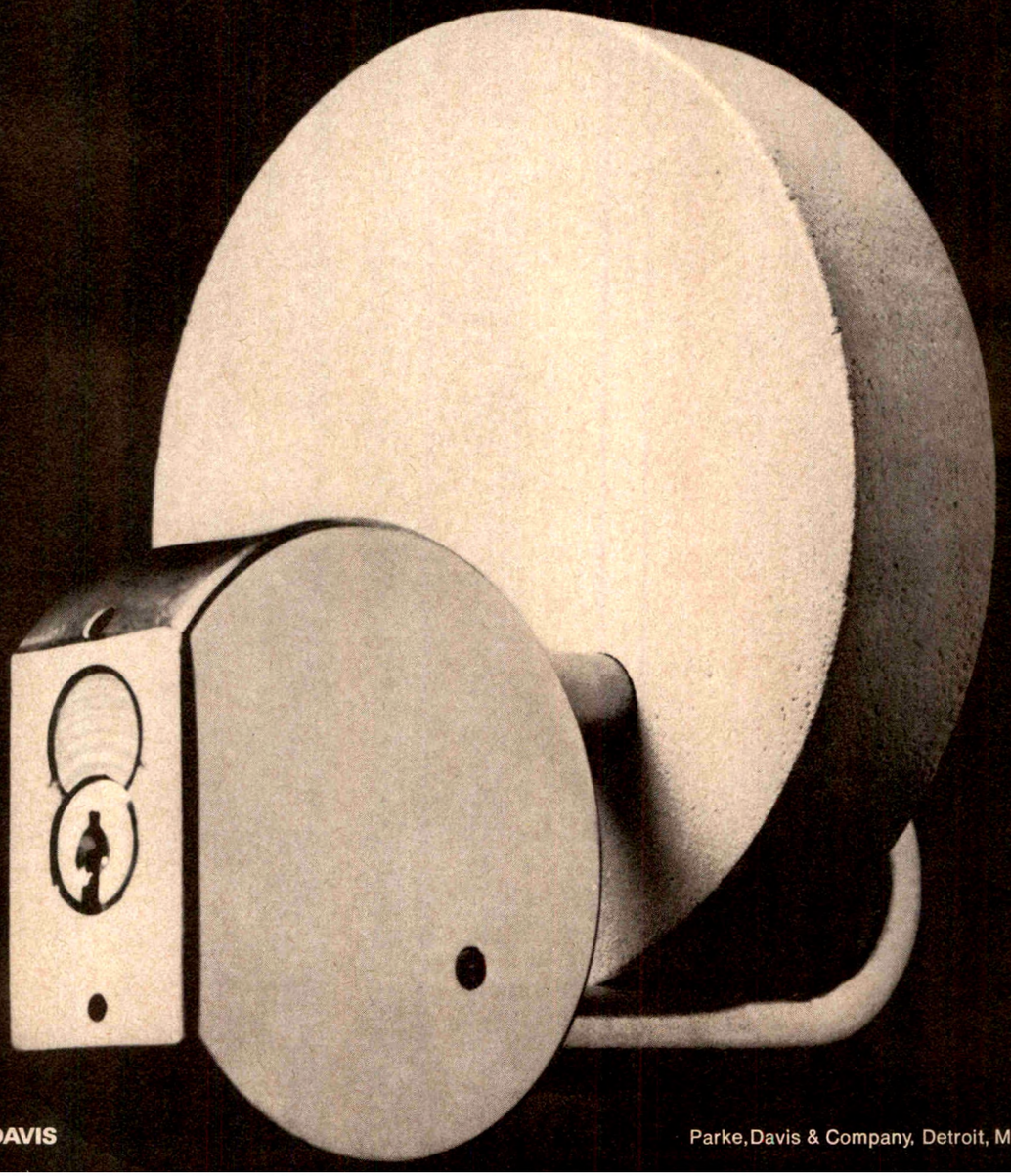

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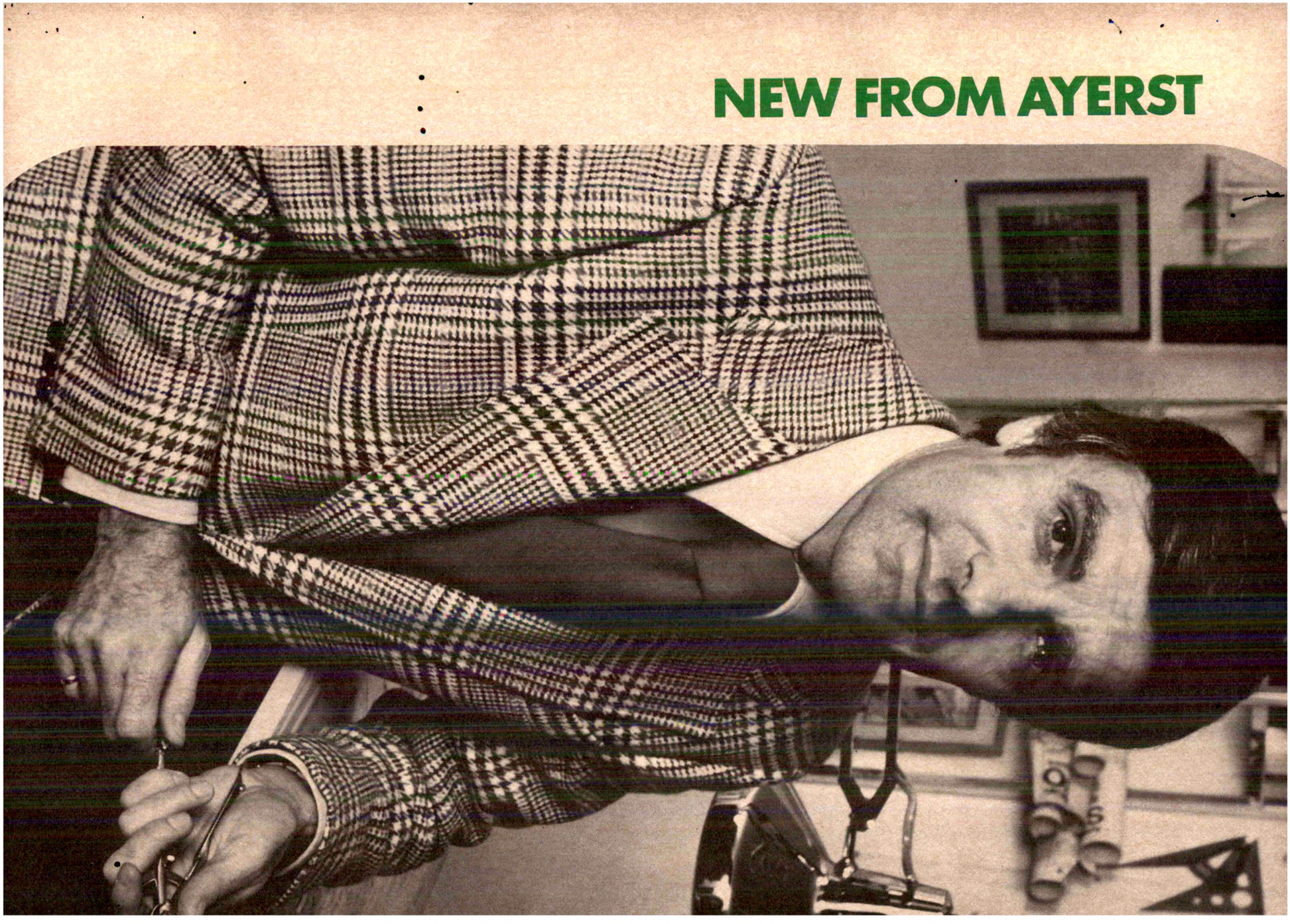

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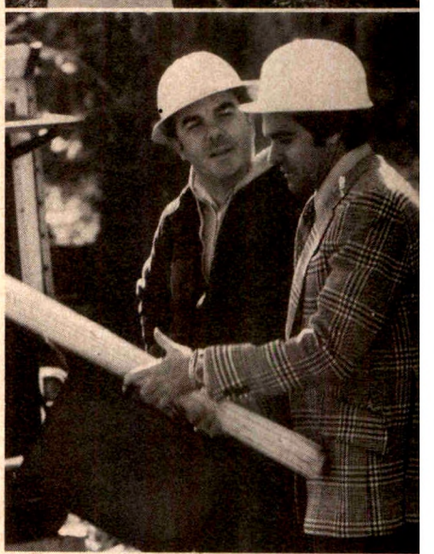

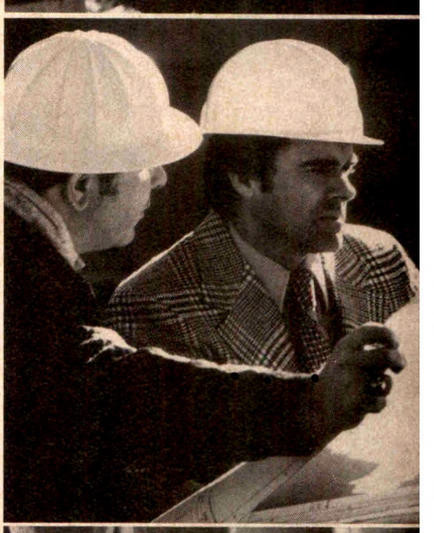

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DIUCARDIN is indicated in severe edema during pregnancy. (See WARNINGS)

DIUCARDIN is indicated in the treatment of edema due to various forms of renal dysfunction, *e.g.* nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CONTRAINDICATIONS: Anuria, oliguria. Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis. **Central Nervous System:** dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

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References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet *2*:311 (Sept.) 1959.

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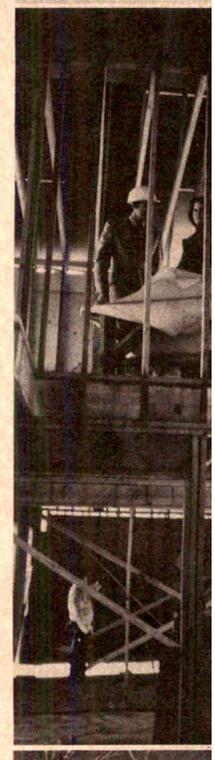

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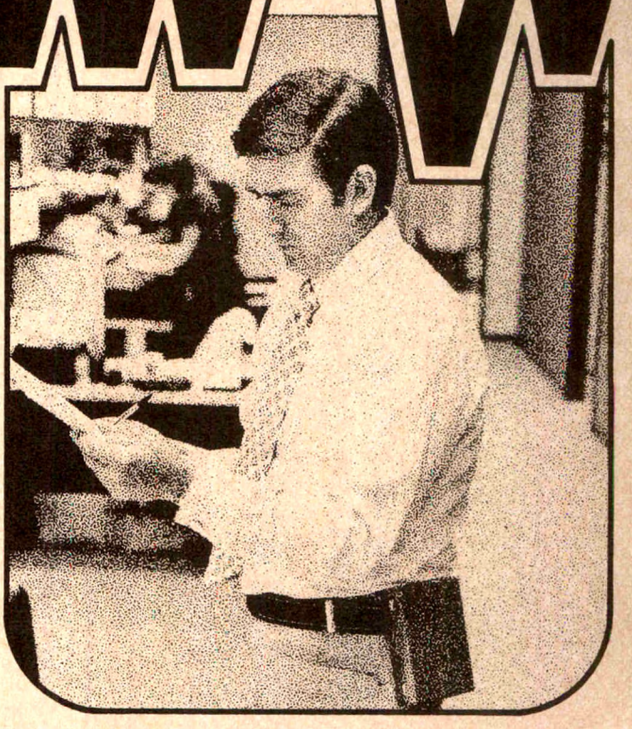

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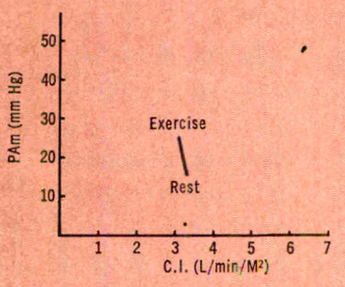
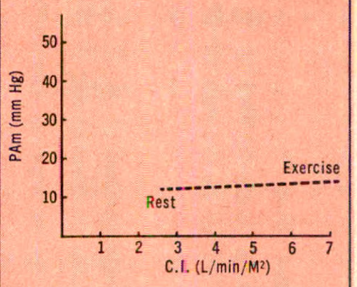
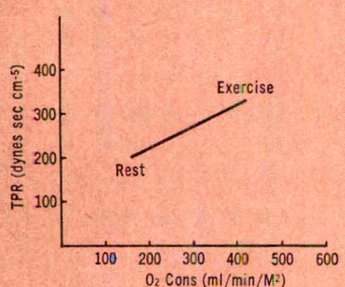
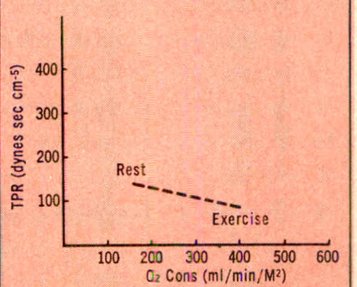
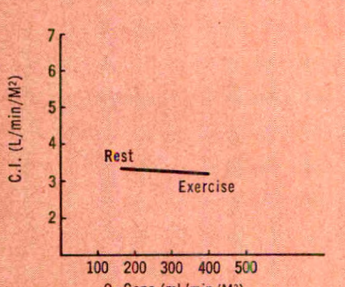
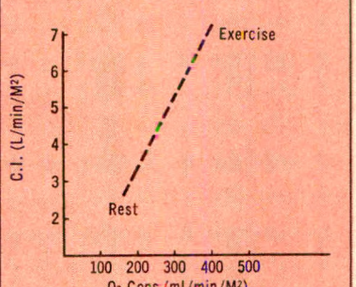
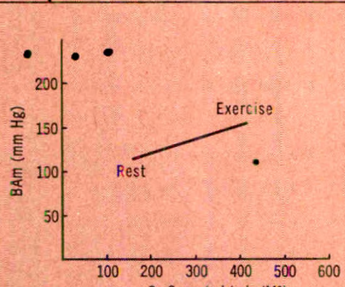
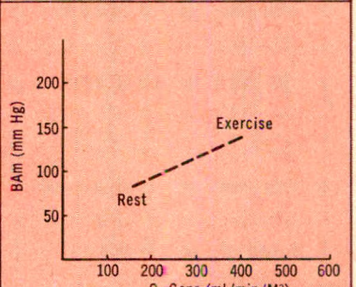
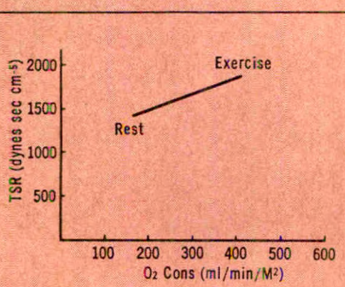
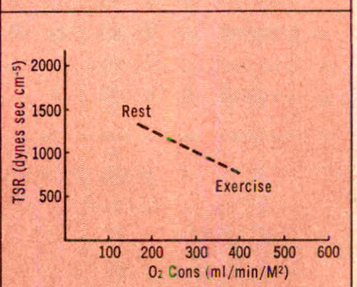
BEFORE MEDICATION		AFTER 5 mg. ISORDIL SUBLINGUAL (isosorbide dinitrate)
	PULMONARY ARTERY (MEAN PRESSURE)	
	TOTAL PULMONARY RESISTANCE	
	CARDIAC INDEX	
	BRACHIAL ARTERY (MEAN PRESSURE)	
	TOTAL SYSTEMIC RESISTANCE	

IN ANGINA PECTORIS*

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday stress

ISORDIL® SUBLINGUAL
(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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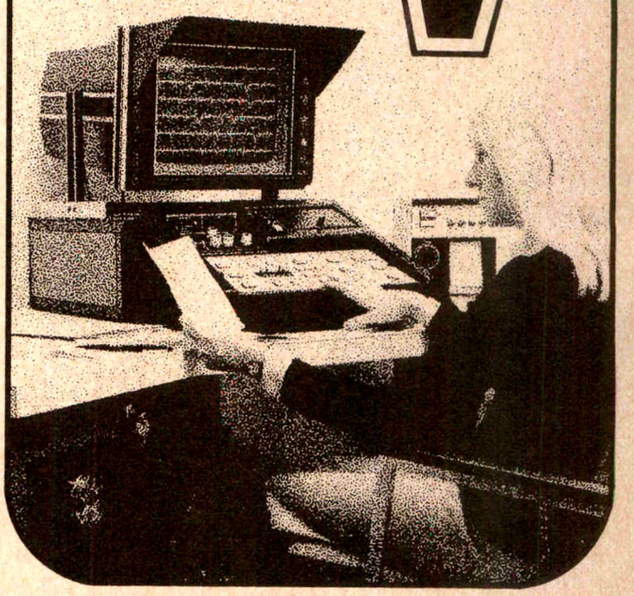
DEDICATED TO IMPROVING THE QUALITY OF LIFE, THROUGH MEDICINE

Adapted from: Kasparian H, Najmi M, Likoff W: Laboratory Evaluation of Coronary Artery Disease. Scientific Exhibit, AMA Convention, Chicago, Ill, June 1966.

We'll lend your patient an ear... and you a hand.



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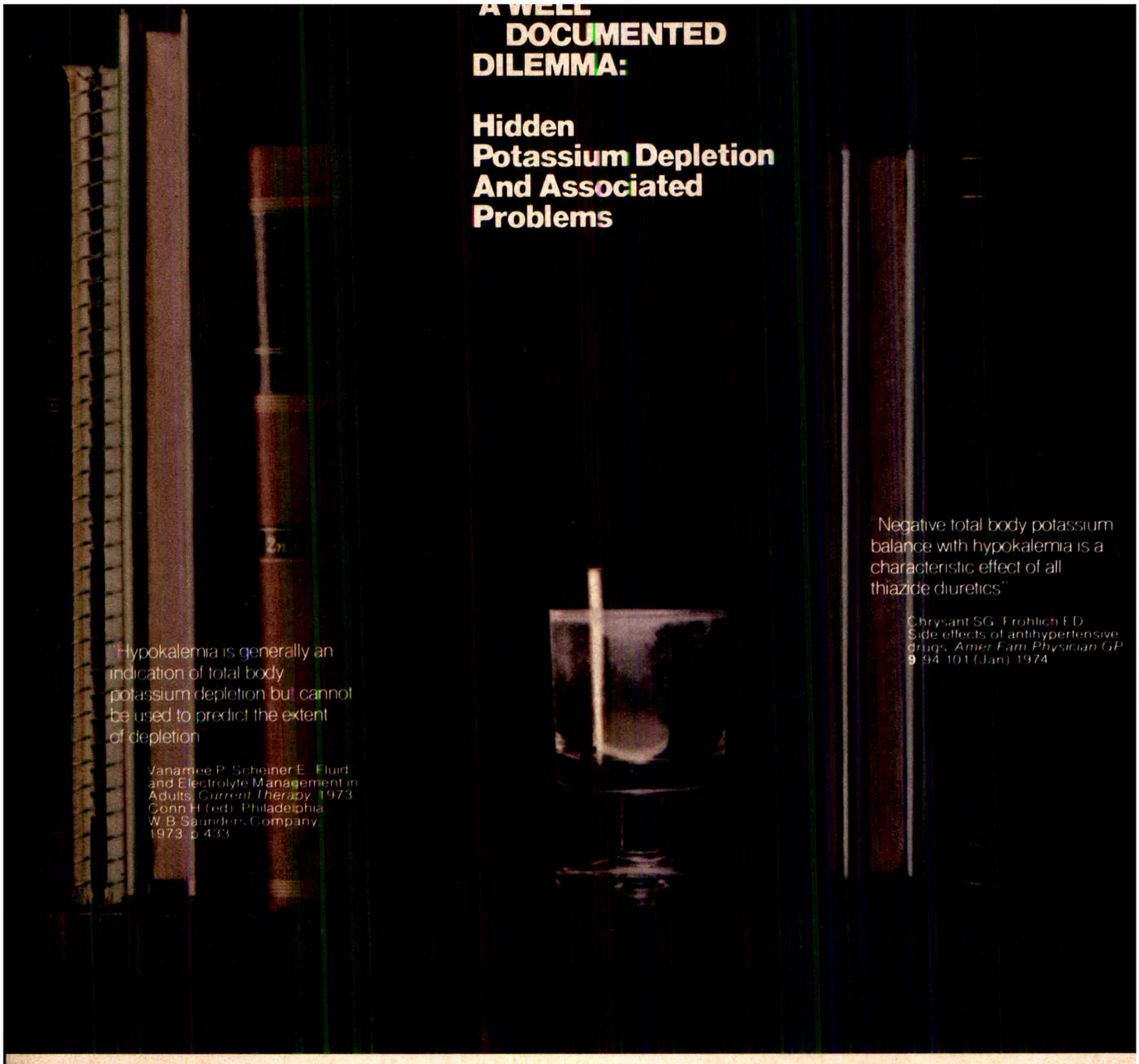

A WELL DOCUMENTED DILEMMA:

Hidden Potassium Depletion And Associated Problems

"Hypokalemia is generally an indication of total body potassium depletion but cannot be used to predict the extent of depletion."

Vanamee P, Scheiner E. Fluid and Electrolyte Management in Adults. *Current Therapy* 1973. Conn H (ed). Philadelphia. W.B. Saunders Company. 1973. p 433.

"Negative total body potassium balance with hypokalemia is a characteristic effect of all thiazide diuretics."

Chrysant SG, Frohlich ED. Side effects of antihypertensive drugs. *Amer Fam Physician GP* 9:94-101 (Jan) 1974.

a simple answer to the hidden potassium dilemma

K+LORVESS®

effervescent tablets

Each tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., L-lysine hydrochloride 0.913 g.

THE BALANCED BENEFIT
POTASSIUM AND CHLORIDE SUPPLEMENT
1:1 ratio K^+ and Cl^- in solution

GOOD TASTING KLORVESS OFFERS WHAT YOU AND YOUR PATIENT WANT: CONVENIENT POTASSIUM SUPPLEMENTATION WITH NO EXTRA CALORIES

- SIMPLE TO TAKE—Tablets dissolve in 3-4 oz. cold water
- EFFERVESCENT SOLUTION—Reduces chance of G.I. irritation.
- UNIT DOSE CONVENIENCE—Tablets individually foil wrapped

KLORVESS®
effervescent tablets

Description: Each dry effervescent tablet contains 20 mEq. each of potassium and chloride supplied by potassium chloride 1.125 g., potassium bicarbonate 0.5 g., L-lysine hydrochloride 0.913 g. Solution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate, and L-lysine hydrochloride.

Indications: For prevention or correction of potassium depletion and hypokalemic alkalosis. Especially useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps, and hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each tablet completely in the stated amount of water.

Adverse Reactions: Vomiting, diarrhea, nausea and abdominal discomfort may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, and tall, peaked T waves.

Dosage and Administration: Adults: 1 tablet (20 mEq. each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water 2 to 4 times daily depending upon the requirements of the patient. The approximate minimum adult daily requirement of potassium is 40 mEq. Deviations from this recommendation may be indicated, since no average total daily dose can be defined but must be governed by close observation for clinical effects. **NOTE: Klorvess should be taken with meals.**

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under Contraindications. Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia:

1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300 to 500 ml. in an hour.
2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.)
3. Hemodialysis and peritoneal dialysis.
4. The use of potassium-containing foods or medicaments must be eliminated.

In cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: 60 Tablets (2 Rx Units of 30 effervescent tablets each). Each tablet is individually foil wrapped.

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If only patients would confess.

Your low-sodium patients may not be telling all. It's not that easy to confess to their doctor that, in actuality, they're letting salt sneak back into their diets.

Cravings & rationalizations.

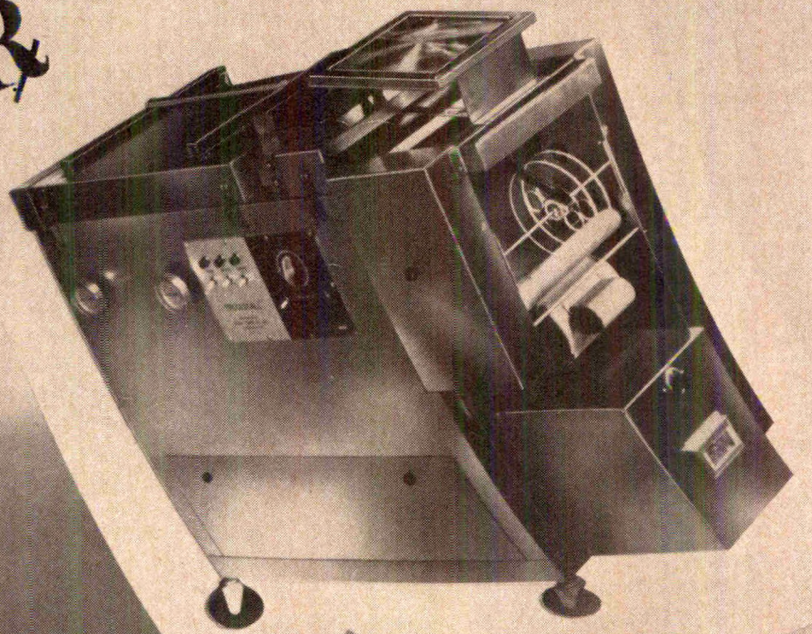
But the blandness of the low-sodium diet may have been more than they could stand, over time. So they summon their healthy powers of rationalization—with unhealthy results.

You might avert these lapses by suggesting, at the start, Adolph's Salt Substitute. It's America's best-selling brand—perhaps because it's the best tasting way to enhance the natural flavors of food. It can improve your patients' zest for eating. And reduce confessions.

Added benefits: Adolph's can be used in cooking just like ordinary salt. It's also a source of supplemental potassium.

Samples? Please write: Jeannette Frank, c/o Adolph's Ltd., Box 828, Dept. SM, Burbank, California 91503.

Processall gives you two keys to accurate diagnosis in Cine Fluorography.



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No wonder major medical centers and hospitals are now using Processall. For more information contact us, or your nearest Oscar Fisher dealer.

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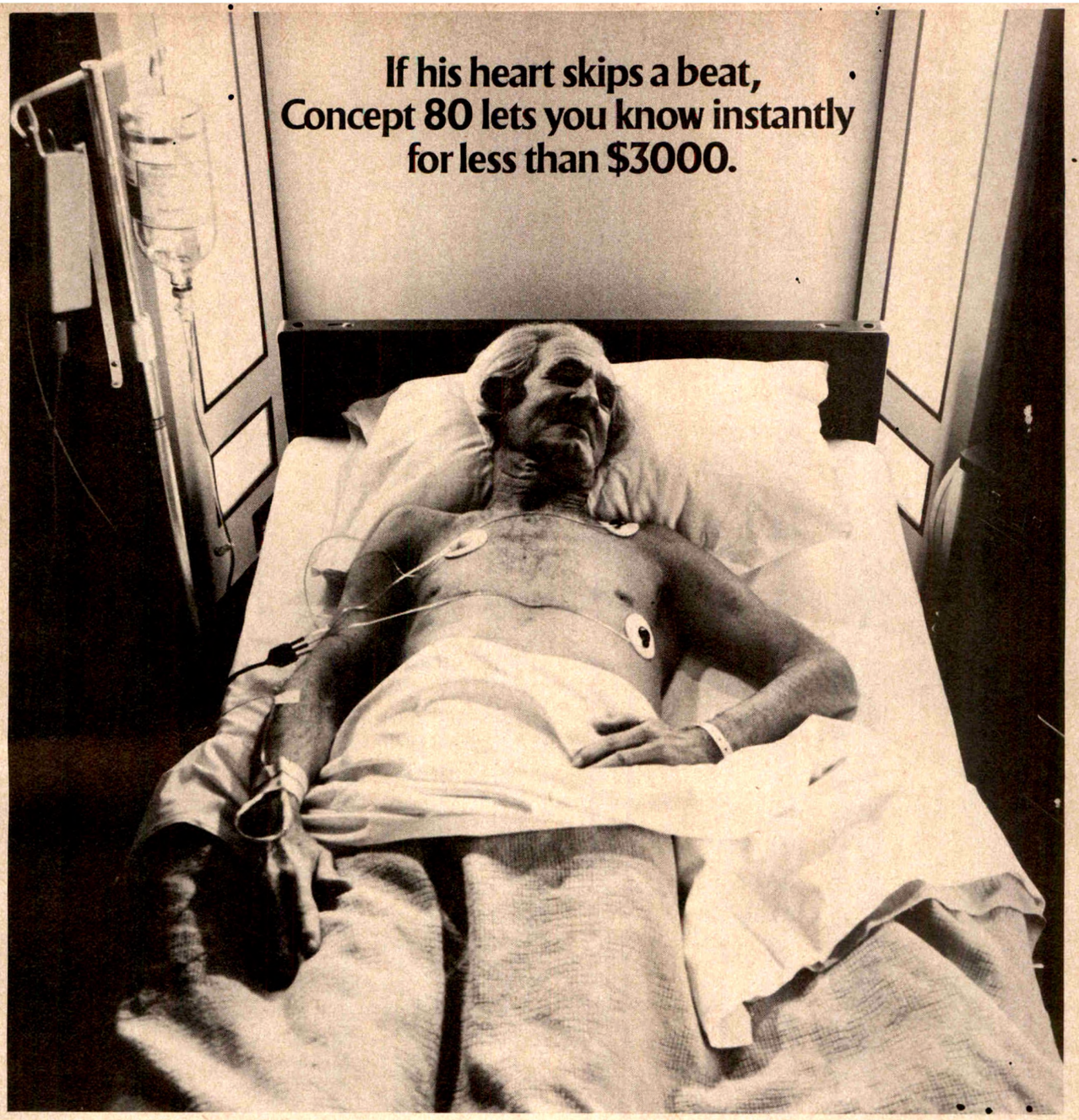
If his heart skips a beat, Concept 80 lets you know instantly for less than $3000.



A nurse can't watch the monitor every minute of the day. But with Concept 80, it isn't necessary. Unlike other cardiac monitoring systems it offers arrythmia recognition at every bed. And it's the only one that does it for less than $3000 a bed.

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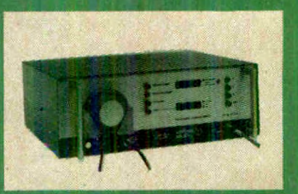
This lifesaving system is composed of five bedside units and a console which can be expanded to monitor up to 20 patients simultaneously. Concept 80's modular construction is easily connected to your existing equipment.

The system is available with either isolated preamplifier at bedside, or FCC approved telemetry for ambulatory patients. With this flexibility, you're able to offer more patients the kind of surveillance formerly reserved for intensive care and cardiac wards.

Concept 80. Now there's a cardiac monitoring system you can afford.

For more information, call Rex McLaughlin (714) 988-2557, or write Lockheed Concept 80, P.O. Box 33, Ontario, Ca. 91761. Lockheed offers immediate delivery.

Lockheed Concept 80



Vitatron Medical upgrade pacemaker reliability

Vitatron Medical now have upgraded the reliability of their pacemakers by application of a new HgO-Zn battery. This battery was specially designed for pacemakers and has a higher energy density and a better dependability.

Battery failure rate is no more than 0.05%/1000h. This new development, together with the battery switch reduces current consumption during transportation and storage to an absolute minimum, increasing pacemaker longevity by 50%.

The small dimensions, light weight, ideal shape and easy electrode connection make the new generation of Vitatron Medical pacemakers extremely easy to implant and assure a minimum of post-operative complications.

The unique intracardial electrode type MIP 2000 with means for fixation to the heartwall allows accurate placement of transvenous electrodes in more difficult cases.

Pacemaker follow-up reliability is achieved by Vitatron Medical's completely analysable pacing system consisting of the VCA pacemaker and the fully automized type MPA 1 digital pacemaker analyzer.

VITATRON MEDICAL

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New from
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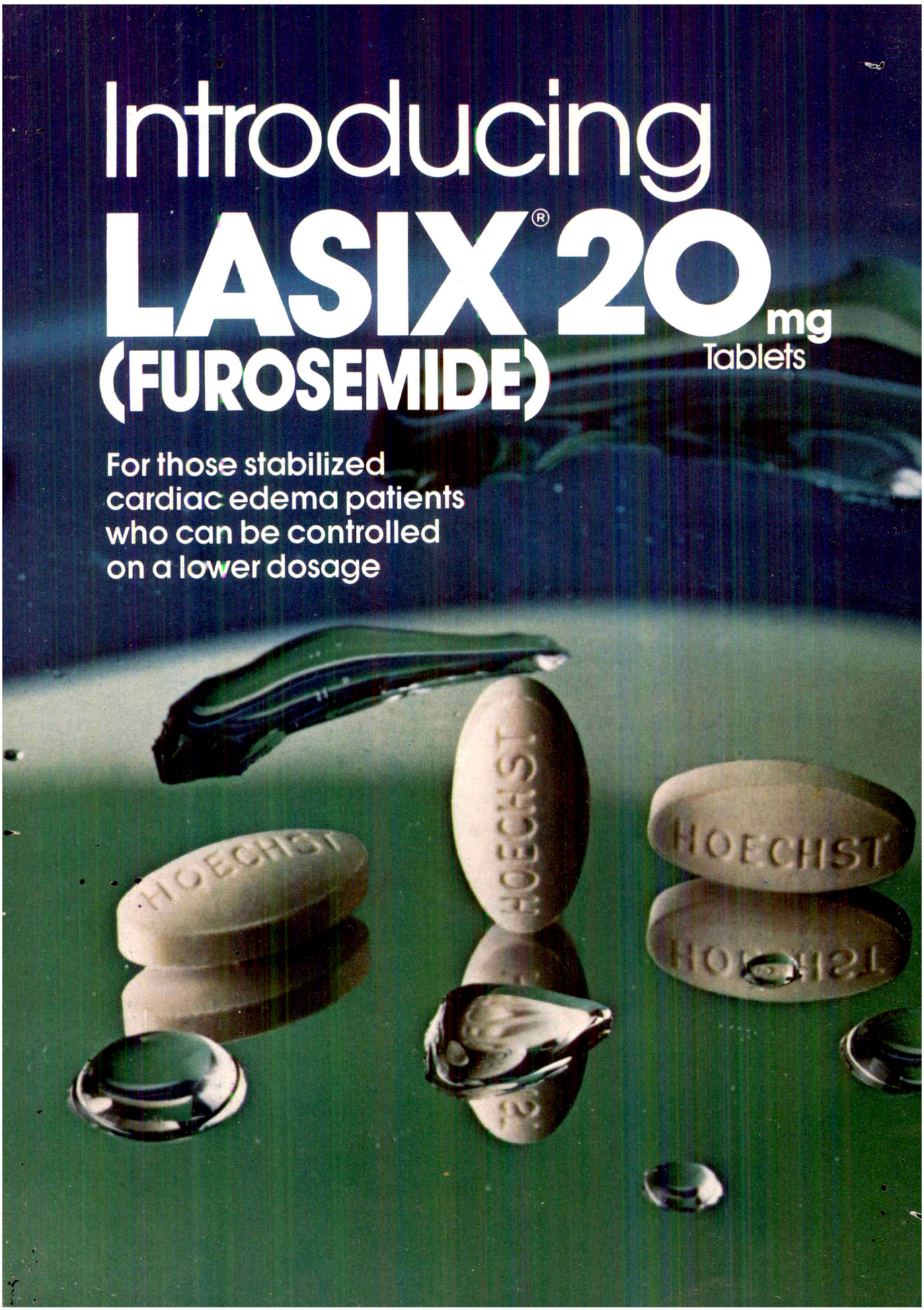
THE LASIX® 20mg (FUROSEMIDE)
MAINTENANCE
TABLET
HOECHST
(Please see last page of this ad
for prescribing information.)


Introducing
LASIX® 20 mg
Tablets
(FUROSEMIDE)
For those stabilized
cardiac edema patients
who can be controlled
on a lower dosage
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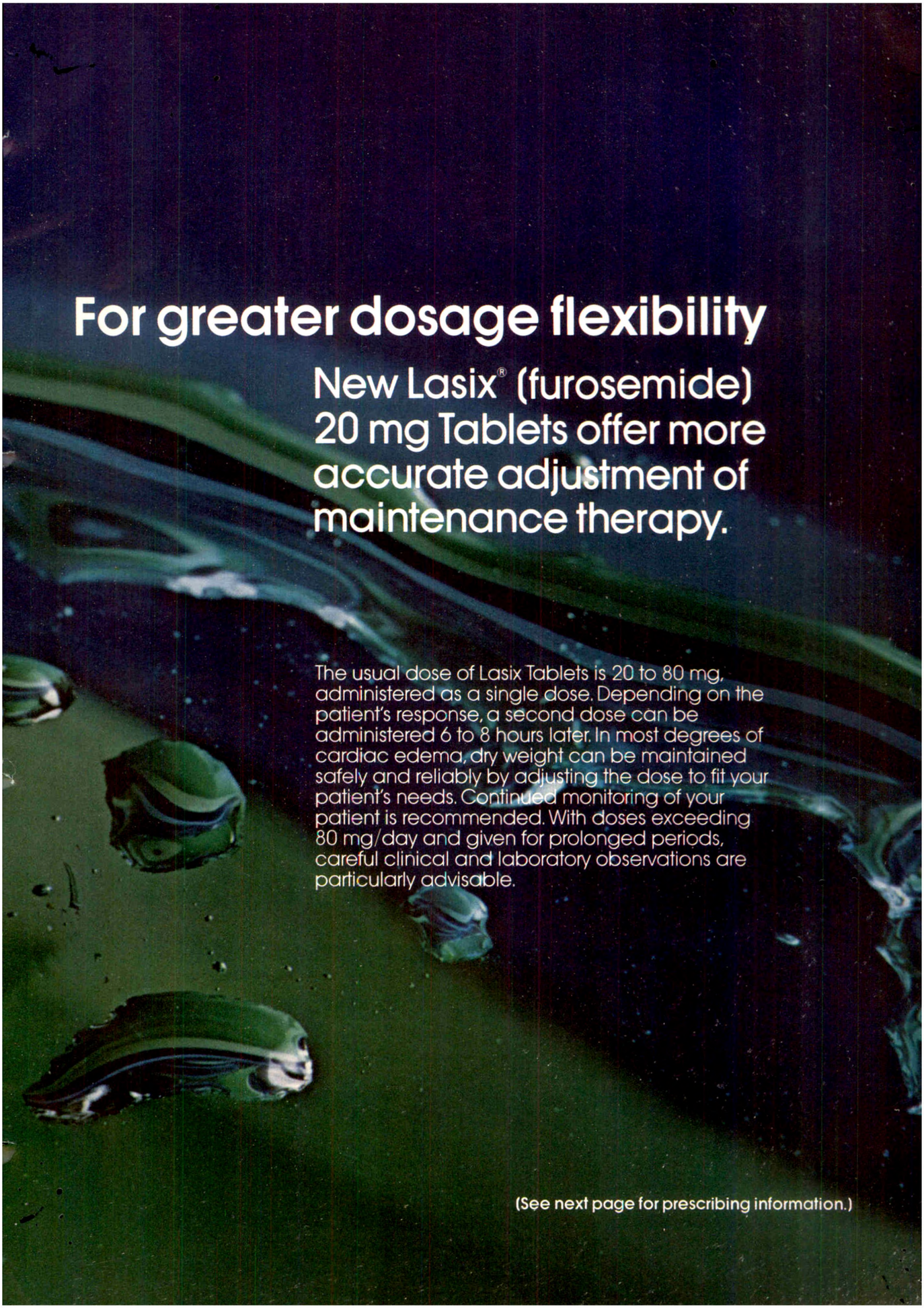
For greater dosage flexibility
New Lasix® (furosemide) 20 mg Tablets offer more accurate adjustment of maintenance therapy.
The usual dose of Lasix Tablets is 20 to 80 mg, administered as a single dose. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. In most degrees of cardiac edema, dry weight can be maintained safely and reliably by adjusting the dose to fit your patient's needs. Continued monitoring of your patient is recommended. With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.
(See next page for prescribing information.)

LASIX® 20 mg (FUROSEMIDE) and 40 mg Tablets

WARNING—Lasix® (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "DOSAGE AND ADMINISTRATION.")

DESCRIPTION—Lasix is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

INDICATIONS—Lasix is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

Hypertension—Lasix Tablets may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of child-bearing potential.

Lasix is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix is contraindicated in patients with a history of hypersensitivity to this compound.

Until more experience is accumulated in the pediatric use of Lasix, children should not be treated with the drug.

WARNINGS—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix.

PRECAUTIONS—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting and/or mental confusion.

In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix is administered, since Lasix potentiates the hypotensive effect of antihypertensive medications.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix precedes its oral use, it should be kept in mind that cases of reversible deafness and tinnitus following the injection of Lasix have been reported. These adverse reactions occurred when Lasix was injected at doses exceeding several times the usual therapeutic dose of 20 to 40 mg.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

It has been reported in the literature that diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix, and it is advisable to discontinue Lasix for one week prior to any elective surgery.

ADVERSE REACTIONS—Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura) may occur. Rare cases of agranulocytosis have occurred which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli (see "WARNINGS"), and acute pancreatitis.

Lasix-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

As far as hyperglycemia is concerned, see "PRECAUTIONS."

DOSAGE AND ADMINISTRATION—The usual dose of Lasix is 20 to 80 mg given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory; e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedules should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). The dose of Lasix may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states. Higher doses are currently under investigation.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 per cent as soon as Lasix is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents; e.g., reserpine, rather than to increase the dose of Lasix.

Until more experience is accumulated in the pediatric use of Lasix, children should not be treated with the drug.

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Permanent Pervenous Transseptal Atrial Pacing

Canine Experiments and a Clinical Case

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Permanent atrial pacing has lain dormant during the last decade because pervenous electrodes usually fail to maintain endocardial contact, and epicardial electrodes require a thoracotomy for implantation. The major advantage is the preservation of synchronized atrioventricular (A–V) contractility. Development of a technique for attaching pacing electrodes to the endocardium through the venous system by an extrathoracic maneuver may permit achievement of reliable long-term atrial pacing pervenously. Canine experiments led to the first clinical application of atrial pacing by way of a transseptal electrode. A Ross needle was modified to carry a 10 mm T-shaped electrode tip across the atrial septum. An intraluminal stylet was used to eject the electrode into the left atrium. The electrode tip was then pulled snugly against the atrial septal endocardium. The hearts of 10 dogs were paced successfully for 3 to 12 months with average thresholds of 6 ma. At autopsy, various degrees of fibrosis constituted the sole pathologic finding. The heart of a 78 year old man with carotid sinus syncope was paced in August 1972, with use of a permanent transseptal atrial electrode and a unipolar pulse generator. The initial threshold was 2 ma and the pacemaker impulse–QRS interval was 180 msec. Consistent long-term atrial pacing may be achieved by attaching a pervenous electrode to the interatrial septum.

Permanent atrial pacing has rarely been used during the last decade because pervenous electrodes usually fail to maintain endocardial contact, and epicardial electrodes require thoracotomy for implantation. The indications have been presented comprehensively by De Sanctis,[1] and the major advantage is the preservation of synchronized atrioventricular (A–V) contraction in patients with cardiac insufficiency who require artificial pacing.

The attachment of pacing electrodes to the endocardium through the venous system by an extrathoracic maneuver is a new concept that invites the development of new techniques to achieve reliable long-term atrial pacing pervenously. A series of canine experiments led to the first clinical application of atrial pacing by the use of a transseptal electrode, both reported here.

Methods and Materials

The feasibility of pacing canine atria by attaching a barb-tipped electrode to the endocardium pervenously has been described earlier.[2] A high rate (20 percent) of hemopericardium was observed after atrial penetration. Because the atrial free wall is notably delicate and thin, the interatrial septum was selected as the safest location for electrode fixation. Bleeding that might occur at this site would be intracardiac, and small secondary septal fenestrations are known to be hemodynamically inconsequential.[3]

A no. 16 gauge Ross transseptal diagnostic catheterization needle[4] was modified to carry a T-shaped electrode tip and conducting wire across the septum (Fig. 1). The electrode was fabricated by connecting a multistrand

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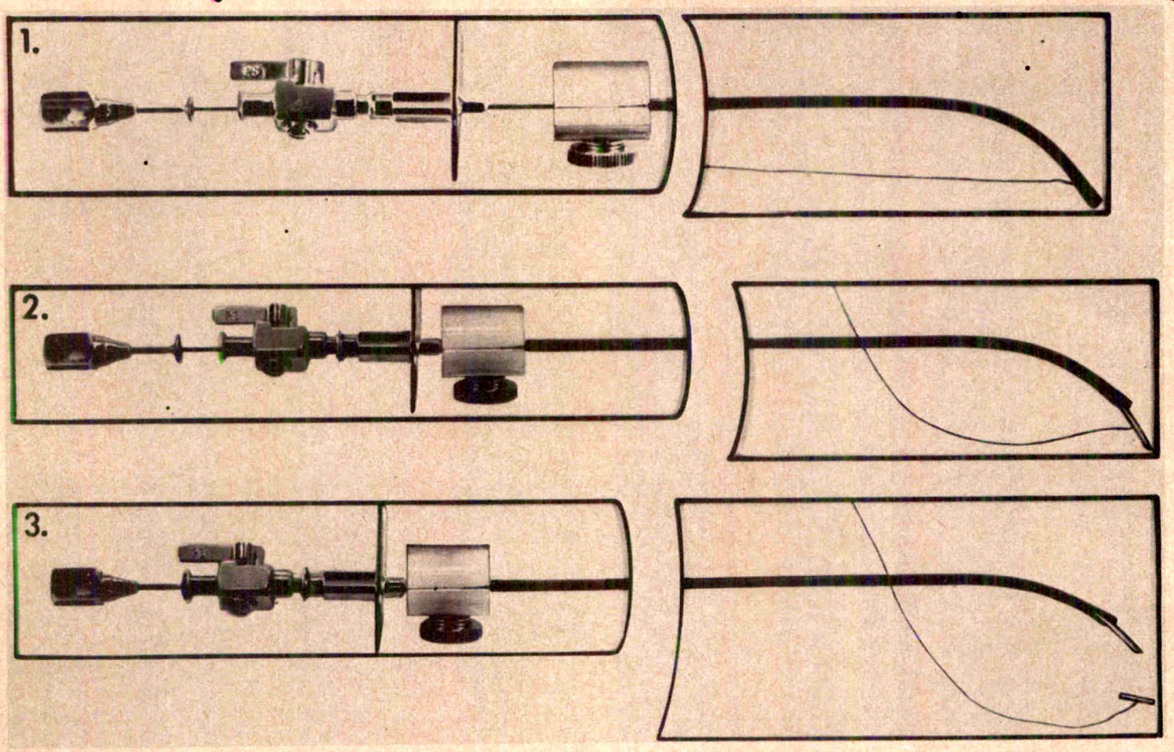

FIGURE 1. The transseptal electrode. **1,** the electrode fixing apparatus assembled. **2,** the septum is punctured by releasing the stop-screw and advancing the needle. **3,** the electrode is ejected by the intraluminal probe shown at the needle's hub.

steel wire (Davis & Geck, 12569-60, Electrode) through a hole in the midsection of a 10 mm cylinder of 20 gauge steel tubing at a 90° angle by a cold press technique. For optimal contact, the Teflon® insulation was removed for a distance of 2 cm from the tip. A 7 mm slit was made down the inner curve of the needle and its protecting catheter to accommodate the conducting wire. A broad plastic stop-screw was created to clasp and stabilize the needle and catheter proximally, thus to prevent pre-emergence of the needle, should the catheter slide back, and of the electrode, should the catheter slide forward.

The atrial septum was approached through the right femoral vein and the fossa ovalis located beneath the limbic edge by fluoroscopy and palpation, as described by Bloomfield and Sinclair-Smith.[3] After septal puncture, an intraluminal probe served to eject the electrode tip into the left atrium. The electrode fixing apparatus was then removed and the electrode tip pulled snugly against the septum by gentle traction.

TABLE I

Pacing Thresholds (in milliamperes)

	Months After Implantation				
Dog no.	0	3	6	10	12
1	1	3			
2	1	12	12		
3	3	5	8		
4	3	8	8		
5	1	3	3		
6	3	5	8		
7	5	12	12	12	
8	3	5		8	8
9	3	12	3	5	5
10	12	5	5	5	5

Results

Animal Experiments

Initial experiments indicated that to achieve safe electrode placement consistently it was necessary to increase the distal angle of the Ross needle from 15° to 35° and to select dogs weighing more than 45 kg. When the unmodified needle was used in small dogs, penetration of the roof of the right or left atrium usually occurred.

Ten dogs were observed for several months after electrode implantation to determine pacing thresholds and pathologic changes at autopsy. The proximal end of the electrode was coiled subcutaneously at the venous cut-down site between threshold tests. Average pacing thresholds increased from 3.5 ma initially to 7.2 ma several months after implantation (Table I). At autopsy, the electrode was firmly affixed in each animal and could not be removed manually. Various degrees of fibrosis on either side of the septum constituted the sole pathologic finding. On the left, the tip was partially or completely endothelialized in all animals (Fig. 2); on the right, a tuft of endothelium surrounded the electrode for a distance of 3 to 15 mm away from the septum (Fig. 3).

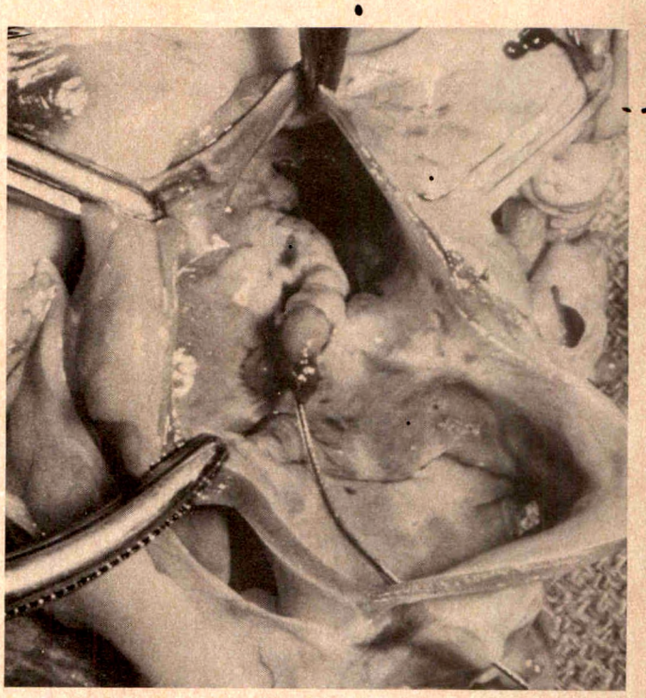

FIGURE 2 (left). The electrode tip endothelialized to the left atrial septum 3 months after implantation.
FIGURE 3 (right). The electrode endothelialized to the right atrial septum 12 months after implantation.

Clinical Case

A 78 year old man with carotid sinus syncope was evaluated for permanent pacing. Gentle carotid massage produced periods of asystole extending up to 9 seconds. Administration of atropine failed to block the hypersensitive reflex. Marked cardiomegaly, antecedent heart failure and normal A–V conduction prompted the conclusion that atrial rather than ventricular pacing would be most beneficial. In August 1972, after the animal experiments, a unipolar electrode was attached to the interatrial septum by way of the right femoral vein under local anesthesia and fluoroscopic guidance. A chest roentgenogram and gentle cardiac pulsations transmitted through the electrode confirmed its desired location and fixation. Electrocardiograms documented atrial capture at a pacing threshold of 2 ma and a pacemaker impulse–QRS interval of 180 msec (Fig. 4). The electrode was then attached to a Merc pulse generator which was implanted subcutaneously in the right lower abdomen. The patient has remained asymptomatic, and carotid massage no longer induces asystole. Serial electrocardiograms have shown a mixture of normal sinus rhythm at rates between 75 and 100 beats/min and artificial A–V pacing at 72 beats/min.

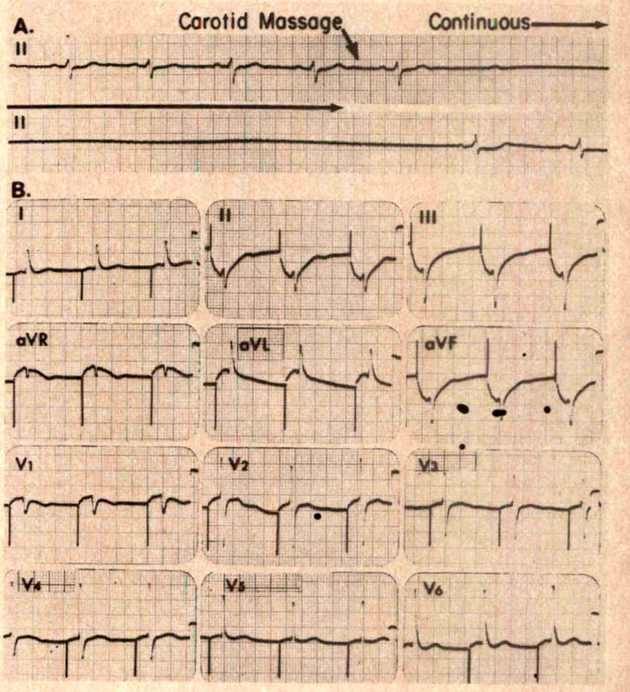

FIGURE 4. The electrocardiogram during and after carotid sinus massage **(A)** and atrial pacing **(B)** in clinical case.

Discussion

Synchronized A–V contraction should be preserved in the treatment of symptomatic bradyarrhythmias with an ideal pacemaker system.[5] Coordinated contractions can be achieved in patients with a "sick sinus" node syndrome and intact A–V conduction—including patients with carotid sinus syncope—by the use of a single electrode attached to the atrium. In patients with A–V block, pacing may be performed synchronously[6] with atrial sensing or sequentially[7] with atrial and ventricular stimulation, using a pair of electrodes.

Coordinated A–V pacing is not currently provided for most patients, in part because atrial pervenous electrodes lack stability and fail to maintain endocardial contact. Free-floating electrodes positioned at various locations inside the right atrium have proved uniformly unreliable for long-term pacing.[8] Three innovations designed to stabilize atrial electrodes have been reported with variable results.

Available techniques for permanent atrial pacing: The coronary vein offers a convenient narrow passageway leading off the atrium which may be cannulated for pacing. Successful, although inadvertent, pacing from this site was reported simultaneously by Moss et al.[9] in this country and Hunt and Sloman[10] in England in 1968. Subsequently, Kramer and Moss[11] achieved successful long-term results in 10 of 14 patients by electrode catheterization of the proximal portion of the great cardiac vein. Several complications have been reported that relate to the mobility of unattached electrodes, including high thresholds and early pacing failures,[12] electrode migration upstream to the left ventricle with loss of atrial pacing and distressing diaphragmatic stimulation,[13] and migration locally with venous perforation and cardiac tamponade.[14] Coronary sinus pacing has been inconsistent in my experience. In one patient, alternating atrial and ventricular pacing was observed in response to various positions assumed by the patient during the pacing trial. Finally, the coronary sinus is not cannulated easily in many patients. For these reasons, coronary venous catheterization has not gained wide acceptance for long-term atrial pacing.

Curved electrodes that impinge the atrial endocardium have been used,[15] and preformed J-shaped electrodes have been fabricated that may be lodged in the right atrial appendage.[16] A central stylet is used to straighten the J configuration before cardiac cannulation. Such electrodes can be manipulated easily into the appendiceal cavity where they have been used quite successfully for atrial pacing[16,17] and synchronous[18] and sequential[7] A–V pacing in 90 percent of 58 cases reported. Failures resulted from electrode disengagement. In contrast to electrodes placed in the ventricle, electrodes lodged in the atrial appendage do not become endothelialized in most instances. Endothelial fixation was not observed by Smyth et al.[17] at autopsy in any of their 15 dogs after several months of pacing, and electrode fixation to the atrial endocardium has been documented in only one human subject to date. Lacking firm endocardial fixation, this method falls short of the desideratum for flawless atrial sensing and pacing.

Finally, a group from East Germany has described a technique that involves an anchor-tipped electrode extruded into the right ventricle[19] or the atrial appendage,[20] designed to attach itself to the endocardium by one or both of its wings. Successful atrial pacing has been reported in 15 consecutive patients. This innovation approaches the objective of permanent atrial pacing; however, two shortcomings are apparent. First, the anchor-tipped electrode is not attached to a preselected site; fixation is dependent upon one of its wings being snagged on a trabeculation. Second, hemopericardium may result from electrode penetration of the atrial wall, a possibility not appreciated by the clinical observations of the European investigators. Results of animal experiments with the anchor-tipped electrode have not been reported.

Hazards of transseptal atrial pacing: Transseptal left atrial puncture is associated with significant risks; the greatest involves cardiac and aortic perforation with subsequent tamponade and, rarely, death, occurring at a frequency of 2, 1 and 0.3 percent, respectively, among 2,219 cases reported from here[21,22] and abroad.[23] Other hazards include femoral thrombophlebitis, pulmonary and systemic embolization, retroperitoneal hemorrhage and arrhythmias. Transseptal puncture is not a simple procedure. Unsuccessful results because of technical difficulties have been reported in 5 percent of 454 patients.[23] These difficulties and complications must be weighed against the morbidity, mortality and greater expense involved in a limited thoracotomy whereby epicardial electrodes may be sutured directly to the atrium.

A safety feature has been added to the Ross technique[4,22] in the method described here to minimize the risks of cardiac and aortic perforation. During preliminary experiments, pre-emergence of the needle and cardiac perforations occurred in several dogs when the operator attempted to secure the catheter proximally with one hand while manipulating the needle into position against the fossa ovalis with the other. These results led to the development of a stop-screw (Fig. 1) to stabilize the needle inside its protecting catheter until the moment of transseptal puncture. Subsequently, cardiac perforations were not observed.

Pacing thresholds: Elevated and variable pacing thresholds found in these experiments were unexpected (Table I). In 8 of 10 dogs thresholds increased with the passage of time; in the other two dogs, thresholds decreased. The highest thresholds were noted in dogs that had the most fibrosis around the electrode tip and conducting wire at autopsy. Thresholds exceeding 12 ma may be excessive for certain implantable pulse generators available today. Use of smaller electrode tips may result in lower thresholds and less fibrosis. The surface area of an electrode is directly related to the energy required for pacing.[8,24]

Clinical implication: The prevailing concept that permanent pervenous atrial pacing is unreliable because of electrode instability[8,16] need not be true. Consistent atrial pacing may be achieved by attaching pervenous electrodes to the interatrial septum. Further experimental and clinical experience is needed to establish the long-term reliability and safety of this new technique.

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Evaluation of Patients with Pulmonary Atresia and Intact Ventricular Septum by Double Catheter Technique

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Accurate definition of the site and length of the atretic segment in the patient with pulmonary atresia and intact ventricular septum is of prognostic and surgical significance. A double catheter technique was developed to allow precise localization of the site of atresia, whether valvular, infundibular, or both. Simultaneous opacification of the pulmonary artery by way of the ductus arteriosus or systemic to pulmonary arterial anastomosis by one catheter and the right ventricle by the second catheter was accomplished in five patients with pulmonary atresia, severe hypoplasia of the right ventricle and intact ventricular septum. The patients were 2 days to 17 months of age and weighed 3,200 to 9,200 g at the time the technique was applied. In these patients, the site of atresia proved to be valvular in one, and both valvular and infundibular in four. The double catheter technique is also applicable to patients with ventricular septal defect and acquired or congenital pulmonary atresia who have had palliative shunts, and to patients with complex transpositions and pulmonary atresia.

Although pulmonary atresia with an intact ventricular septum is an uncommon and serious type of cyanotic congenital heart disease, early recognition,[1–3] accurate diagnosis[4–6] and aggressive surgical therapy[7–14] have led to increased salvage of infants with this condition.

The size of the right ventricular cavity and site of atresia, whether valvular, infundibular, or both, have obvious important prognostic and surgical implications. Although several avenues of surgical therapy are currently in use,[7–14] a direct attack on the valve combined with a systemic to pulmonary arterial anastomosis has been advocated by some in those patients with pulmonary atresia and hypoplastic right ventricle.[11]

Although most reports suggest that the pulmonary atresia in patients with an intact ventricular septum is confined to the valvular level,[1,3,11,15,16] Morgan et al.[17] and other investigators[10,12–14] have documented both valvular and infundibular atresia. The observation of combined valvular atresia and either severe infundibular stenosis or atresia has also been common in our experience.

We recently studied five patients with pulmonary atresia and intact ventricular septum using a double catheter technique. The method allows simultaneous opacification of the pulmonary artery and the right ventricle and, hence, precise localization of the site and length of obstruction. In this communication we present this technique and our preliminary results with a discussion of other possible applications.

Patient Selection and Methods

Five patients with pulmonary atresia and intact ventricular septum were studied. All had severe hypoplasia of the right ventricle. The double catheter

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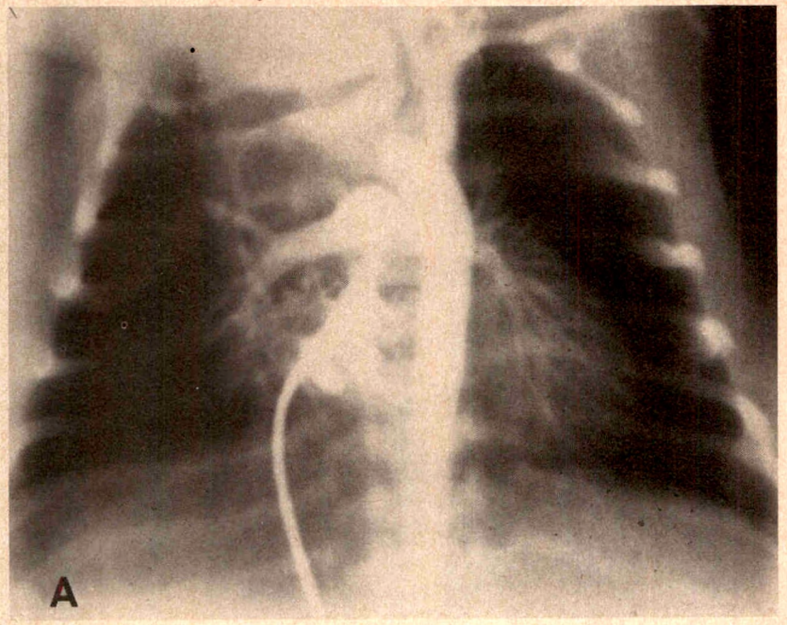

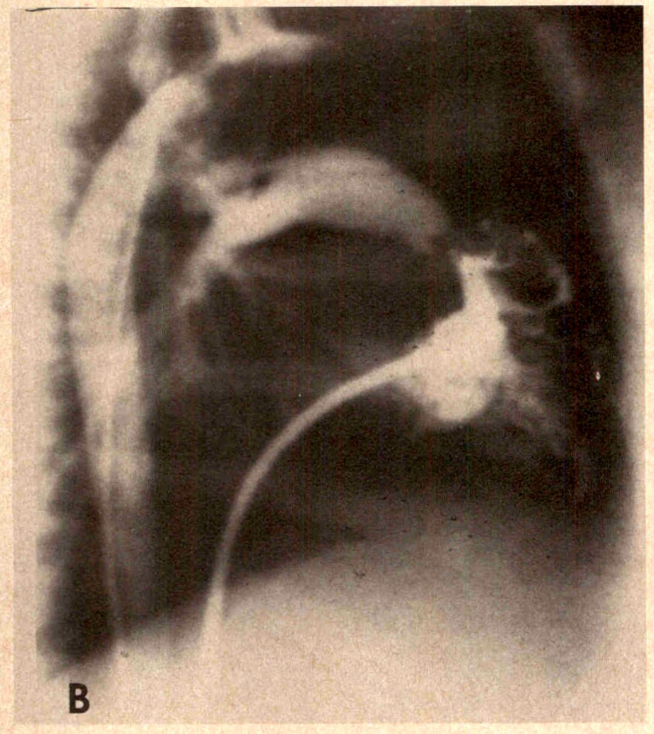

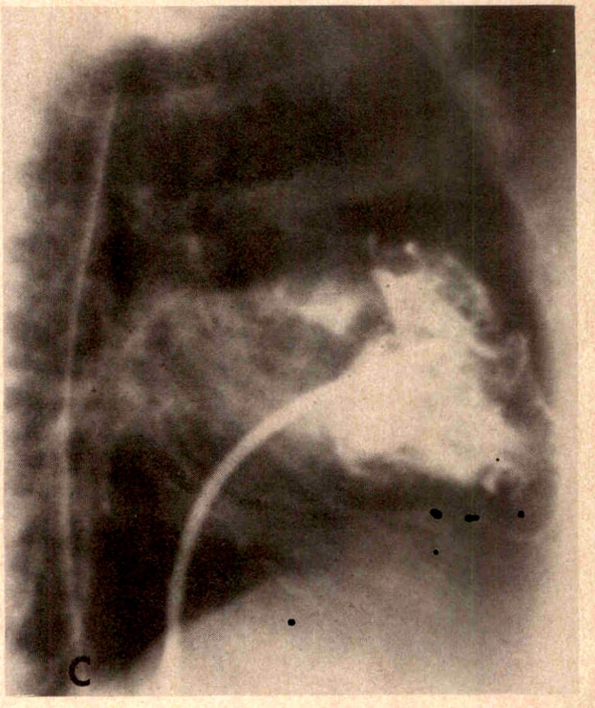

FIGURE 1. A and **B,** simultaneous biplane right ventriculogram and thoracic aortogram in a 2 day old infant weighing 3.2 kg. **C,** later radiograph from the same angiogram in the lateral projection. The early radiographs **(A, B)** demonstrate a small, heavily trabeculated right ventricular chamber with opacification of myocardial sinusoids **(B).** The pulmonary artery is of normal caliber, and retrograde visualization to the level of the atretic valve is noted. The atresia seems primarily valvular, but the distal infundibulum is severely stenotic. As shown in **C,** it is difficult to estimate the length of the atretic segment from a standard right ventricular angiogram.

technique was applied to one newborn infant before performance of a systemic to pulmonary arterial anastomosis, and in the other four patients after the shunt procedures. The patients were aged 2 days and 4, 5 1/2, 6 and 17 months and weighed 3.2, 4.8, 5.3, 4.3 and 9.2 kg, respectively.

At cardiac catheterization, an angiographic catheter was advanced to the right ventricle by the saphenous, femoral or axillary venous approach. In the 2 day old infant, a modified umbilical arterial catheter[18] was advanced through the umbilical artery to the level of the patent ductus arteriosus. In the infant who had previously undergone an ascending aorta to right pulmonary arterial anastomosis, the arterial catheter was positioned in the ascending aorta by way of the right axillary artery. Three patients had undergone a descending thoracic aorta to left pulmonary arterial anastomosis (Potts' shunt). In these patients, the arterial catheter was introduced into the femoral artery and advanced into the pulmonary artery by way of the Potts' communication. Opacification of the right ventricle and pulmo-

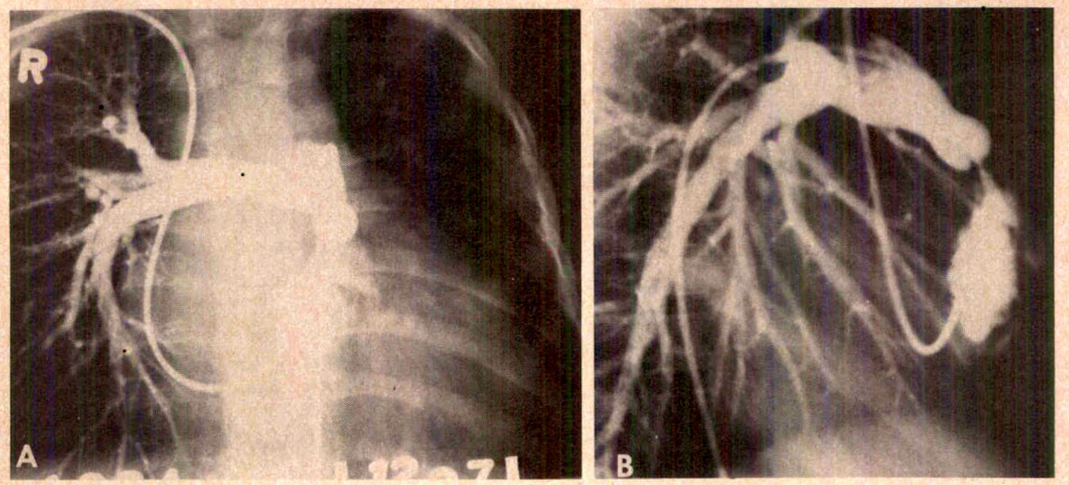

FIGURE 2. A and **B,** simultaneous right ventriculogram and retrograde pulmonary arteriograms (selective catheterization of Potts' anastomosis) in a 17 month old child weighing 9.2 kg. A small right ventricular cavity with a hypoplastic, severely narrowed infundibulum is demonstrated. Excellent opacification of the main and right pulmonary artery is obtained. The left pulmonary artery is not opacified because of rapid washout of blood from the Potts' anastomosis. The pulmonary valvular annulus is minimally narrowed and pulmonary valvular tissue is identified despite atresia. A right ventricular angiogram performed immediately before the double catheterization demonstrated pulmonary atresia but did not define the length or site of the atretic segment.

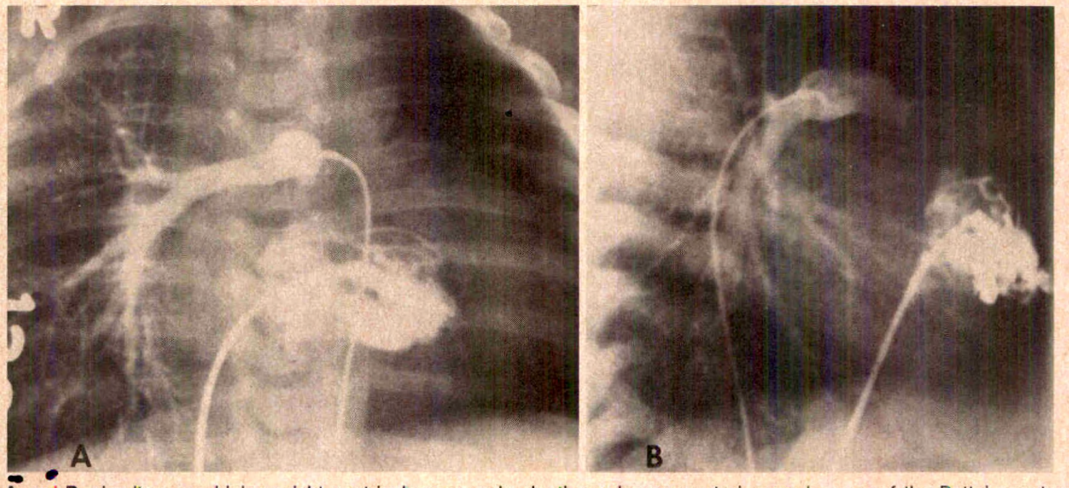

FIGURE 3. A and **B,** simultaneous biplane right ventriculogram and selective pulmonary arteriogram by way of the Potts' anastomosis in a 4 month old infant who weighed 4.8 kg. In contrast to the findings in Figures 1 and 2, a long atretic segment is demonstrated between the pulmonary valve and right ventricle. A simple valvotomy in this patient probably would not be effective.

nary artery was obtained by hand injection of 0.25 to 0.50 ml/kg body weight of contrast material into the right ventricle and simultaneous pressure injection of 1.00 to 1.25 ml/kg of contrast material through the arterial catheter into the pulmonary artery. Serial biplane radiographs were then obtained in the anteroposterior and lateral projections at filming rates of 6 or 12 films/sec for the first 2 seconds.

Results

Successful simultaneous opacification of the diminutive right ventricle and pulmonary artery was accomplished in all five patients. Catheterization of the pulmonary artery from the right ventricle was not possible because of the congenital pulmonary atresia. However, direct catheterization of the pulmonary artery by way of the Potts' communication was performed in three patients.

This technique allowed precise definition of the site and extent of the congenital pulmonary atresia. All of the patients in this study had type I pulmonary atresia with a small or tiny right ventricle.[3] In one patient, the atresia was localized to the valve, but the infundibulum of this patient was severely hypoplastic and narrowed (Fig. 1). In the other four patients, the atretic segment appeared to be both valvular and infundibular, and of considerable length (Fig. 2 and 3). In addition, the proximal main pulmonary artery was absent in one case. Abnormal intramyocardial sinusoid-coronary arterial communications were

demonstrated in all five patients.[19] All five had a hypertensive right ventricle by standard pressure recording.

Discussion

The double catheter technique allows definition of the site and extent of the pulmonary atresia, and in this small series, the method produced no complications. The umbilical artery provides easy access to the descending thoracic aorta in neonates and has been used for some time in catheterization procedures in infants.[20] In older infants, the technique requires cannulation of a peripheral artery. We have recently been using the new system described by White et al.[21] for percutaneous arterial catheterization in the small infant.

Although in many patients with pulmonary atresia and intact ventricular septum, the atretic segment is localized to the valve, our results and the observations of others suggest that this finding is not invariable. A valvotomy alone without infundibulectomy would probably be ineffectual in the patient with both valvular and infundibular atresia, or severe infundibular narrowing. Yet a successful valvotomy in a patient with type I pulmonary atresia and isolated membranous valvular atresia may be beneficial by providing an opportunity for more volume change at less systolic pressure.[11] Furthermore, decompression of the hypertensive right ventricle might lead to diminution of the abnormal intramyocardial sinusoid-coronary arterial communications and their deleterious effects.

Although acquired infundibular atresia has been documented by serial angiocardiography in patients with tetralogy of Fallot,[22,23] this has not been demonstrated in patients with pulmonary valvular atresia and intact ventricular septum. In our four older infants comparison of findings obtained by the double catheter technique with those obtained by standard right ventricular angiography (performed in the neonatal period) showed no substantial changes in the appearance of the right ventricle, thus suggesting that the infundibular atresia was not acquired.

The double catheter technique is also applicable to the study of tetralogy of Fallot and pulmonary atresia, either acquired or congenital, and to complex transpositions with associated pulmonary atresia,[24,25] as well as pulmonary atresia with intact ventricular septum. Accurate definition of the type of pulmonary atresia by this technique may lead to improved surgical results in these difficult cases.

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Echocardiographic Assessment of Cardiac Malposition

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Isolated dextrocardia or isolated levocardia almost invariably indicates the presence of a complex cardiac anomaly. An accurate anatomic diagnosis in patients with these malformations requires knowledge of the atrial position, the relative position of the ventricles (atrioventricular concordancy or discordancy) and the presence or absence of a ventricular septum. Fifteen patients were studied to demonstrate that diagnostic ultrasound, in conjunction with the plain chest roentgenogram, provides a noninvasive method for accurately assessing atrioventricular relations and arrangement of the great vessels, in the presence of isolated discordancy of the cardiac apex. The patients studied were aged 10 months to 17 years; seven had isolated dextrocardia, five had situs inversus totalis, two had isolated levocardia and one had levocardia with abdominal heterotaxy. Thirteen of the 15 patients evaluated by echocardiography underwent cardiac catheterization and angiography. The correct diagnosis was made from the echograms and plain chest roentgenograms alone in 11 of the 13 patients. We conclude that with echocardiography and the knowledge of atrial situs, it is possible to define accurately important anatomic relations before cardiac catheterization in patients with cardiac malposition.

Isolated discordancy of the cardiac apex, whether in situs solitus or situs inversus, almost invariably indicates the presence of a complex cardiac anomaly.[1] Ventricular inversion (levotransposition of the great vessels), single ventricle and atrioventricular valve anomalies are among the most frequent anomalies encountered.[2] An accurate anatomic diagnosis in patients with these lesions requires knowledge of the atrial position, the relative position of the ventricles and the presence or absence of the interventricular septum as well as the arrangement of the great vessels.

The anatomic diagnosis of cardiac defects in patients with cardiac malposition is difficult and depends upon cardiac catheterization and selective angiocardiography. Atrial and abdominal situs may be determined from the tracheobronchial air column on a plain chest roentgenogram.[3] Discordance of the atrial situs with the abdominal viscera rarely occurs.[4] The use of echocardiography in the evaluation of heart disease in adults has been well established[5] and has been successfully applied in many congenital cardiac defects.[6,7]

It is the purpose of this paper to demonstrate that diagnostic ultrasound, in conjunction with the plain chest roentgenogram, can provide a noninvasive method for accurately assessing atrioventricular relations, the presence or absence of a ventricular septum and arrangement of the great vessels in the presence of isolated discordancy of the cardiac apex.

Material and Methods

Case material: Fifteen patients between the ages of 10 months and 17 years were studied by ultrasound; 13 also underwent cardiac catheterization

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Manuscript accepted November 14, 1973.

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TABLE I

Summary of Data in 15 Patients with Cardiac Malposition

Case no.	Age (yr)	Plain Chest Roentgenogram	Echographic Diagnosis	Cineangiographic Diagnosis
1	1 6/12	Dextrocardia, situs solitus	Tetralogy complex	Truncus arteriosus (type II), situs solitus
2	2	Dextrocardia, situs solitus	L-TGV	L-TGV, VSD, PS, situs solitus
3	3 10/12	Dextrocardia, situs inversus	D-TGV	D-TGV, VSD, PS, situs inversus
4	8	Dextrocardia, situs solitus	?	TOF, superiorly displaced LV, situs solitus
5	6 7/12	Dextrocardia, situs inversus	A–V concordance, normally related great arteries	Mirror-image dextrocardia, ASD, VSD
6	7	Dextrocardia, situs inversus	A–V concordance, normally related great arteries	Mirror-image dextrocardia, VSD, PS
7	1 2/12	Dextrocardia, situs solitus	L-TGV	L-TGV, VSD, situs solitus
8	17	Dextrocardia, situs solitus	A–V concordance, normally related great arteries	...
9	11	Dextrocardia, situs inversus	A–V concordance, normally related great arteries	...
10	6 6/12	Dextrocardia, situs inversus	L-TGV	L-TGV, VSD, PS, situs inversus
11	7 8/12	Levocardia, situs inversus	A–V concordance, normally related great arteries	VSD, PS, abdominal situs inversus
12	11 4/12	Levocardia, situs inversus	A–V concordance, normally related great arteries	ASD, VSD, PH, abdominal situs inversus
13	9 8/12	Dextrocardia, situs solitus	L-TGV	L-TGV, situs solitus
14	7 6/12	Levocardia, abdominal heterotaxy	Single ventricle, D-TGV	Single atrium & ventricle, D-TGV, situs ambiguous
15	1 1/12	Dextrocardia, situs solitus	Single ventricle, L-TGV	Single ventricle, L-TGV, situs solitus

ASD = secundum atrial septal defect; A–V = atrioventricular; D-TGV = dextrotransposition of the great vessels; L-TGV = levotransposition of the great vessels; LV = left ventricle; PH = pulmonary hypertension; PS = pulmonic stenosis; RV = right ventricle; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

(see Table I). Seven patients had isolated dextrocardia, five had situs inversus totalis, two had isolated levocardia and one had levocardia with abdominal heterotaxy. The cardiac lesions in the patients with dextrocardia consisted of levotransposition of the great vessels, single ventricle, truncus arteriosus (type II) and one instance of ventricular septal defect with an atrial septal defect. In the latter case, the left ventricle was superior, leftward and anterior to the right ventricle. Of the five patients with situs inversus, two had dextrotransposition of the great vessels, one had a ventricular septal defect with pulmonic stenosis, one had a ventricular septal defect with an atrial septal defect in addition to sequestration of the right lower pulmonary lobe, and one patient had a normal heart. One patient with isolated levocardia had a single ventricle, and the other had a normal heart. The patient with abdominal heterotaxy and levocardia was thought to have a single ventricle with dextrotransposition.

Echocardiographic technique: With patients in a supine position, ultrasound examinations were performed using a Hoffrel Ultrasonoscope (model 101 with model 704 slow sweep accessory). In children less than 1 year of age, a 3.5 or 5.0 megahertz nonfocused transducer with an outer diameter of 0.25 inch was used. In older patients a 2.25 megahertz, 0.25 or 0.50 inch transducer focused at 5 cm was used. A water-soluble gel was utilized to insure an airless contact between the patient's skin and the transducer.

Plain chest roentgenograms were obtained in all patients to determine the position of the cardiac apex and visceral situs. When the apex was to the left, the ultrasound examination began to the left of the sternal border. If the apex was to the right, the examination was begun to the right of the sternal border. Echocardiographic relations assume significance only when the position of the transducer as well as the path of the ultrasound beam are known. These relations are stated in terms of left or right, superior or inferior and anterior or posterior. The sequence of structures examined was as follows: (1) the mitral valve, identified by its continuity with a semilunar valve, (2) the great vessel in continuity with the mitral valve, (3) the tricuspid valve, (4) the second root structure, and (5) the interventricular septum. The positions of the structures present were carefully noted and indicated on a line drawing of the heart and chest cavity. After analysis of the echograms and roentgenograms, a descriptive anatomic diagnosis of the cardiac defect was made. The cineangiogram of each patient was then reviewed and the angiographic diagnosis was compared with the echographic diagnosis.

Results

Tracheobronchial tree and visceral situs: Atrial and visceral situs were determined from the roentgenograms as described by van Mierop et al.[3] Figure 1A is an example of a normal tracheobronchial tree

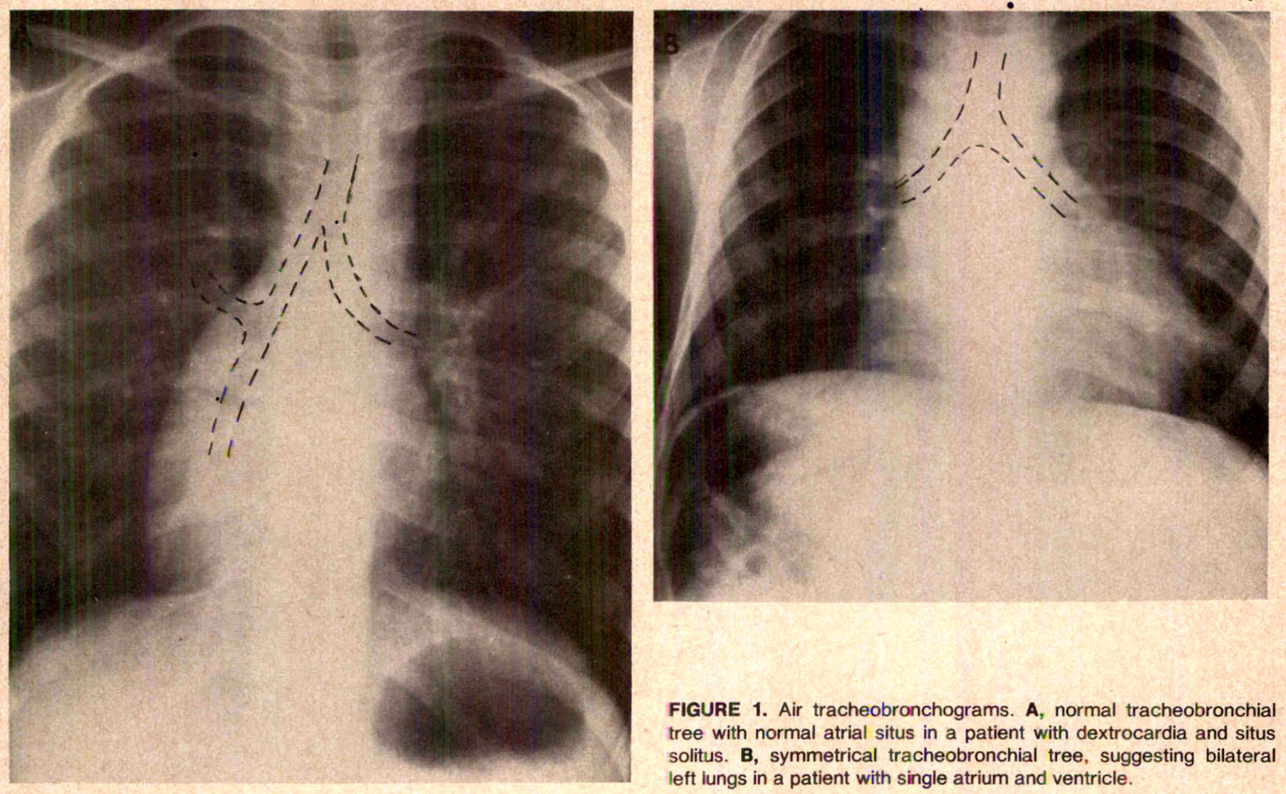

FIGURE 1. Air tracheobronchograms. **A,** normal tracheobronchial tree with normal atrial situs in a patient with dextrocardia and situs solitus. **B,** symmetrical tracheobronchial tree, suggesting bilateral left lungs in a patient with single atrium and ventricle.

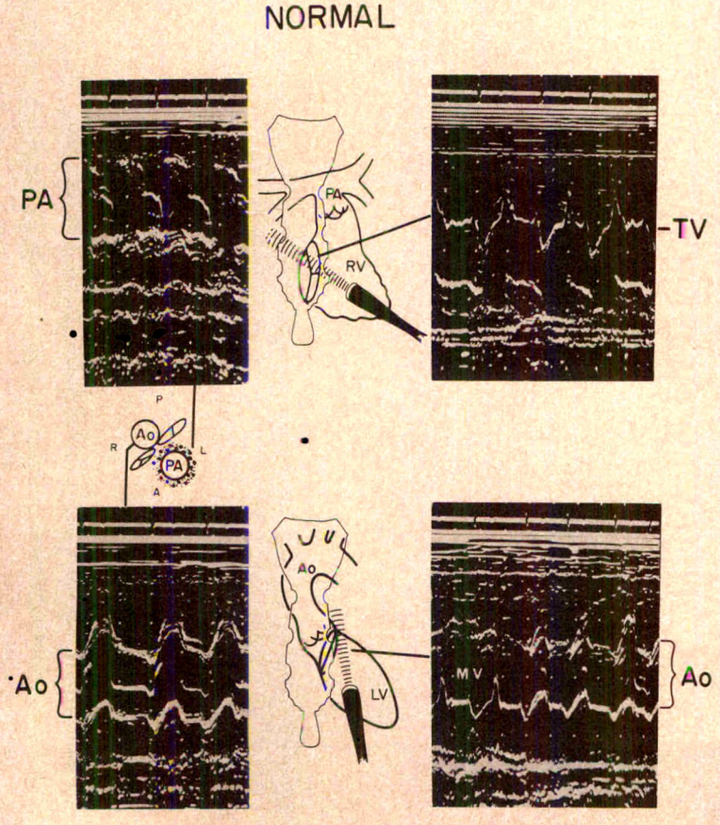

FIGURE 2. Composite picture demonstrating the transducer position for recording the mitral and tricuspid valves in a normal heart. The echograms show the relations of the cardiac structures. A = anterior; Ao = aorta; L = left; LV = left ventricle; MV = mitral valve; P = posterior; PA = pulmonary artery; RV = right ventricle; TV = tricuspid valve.

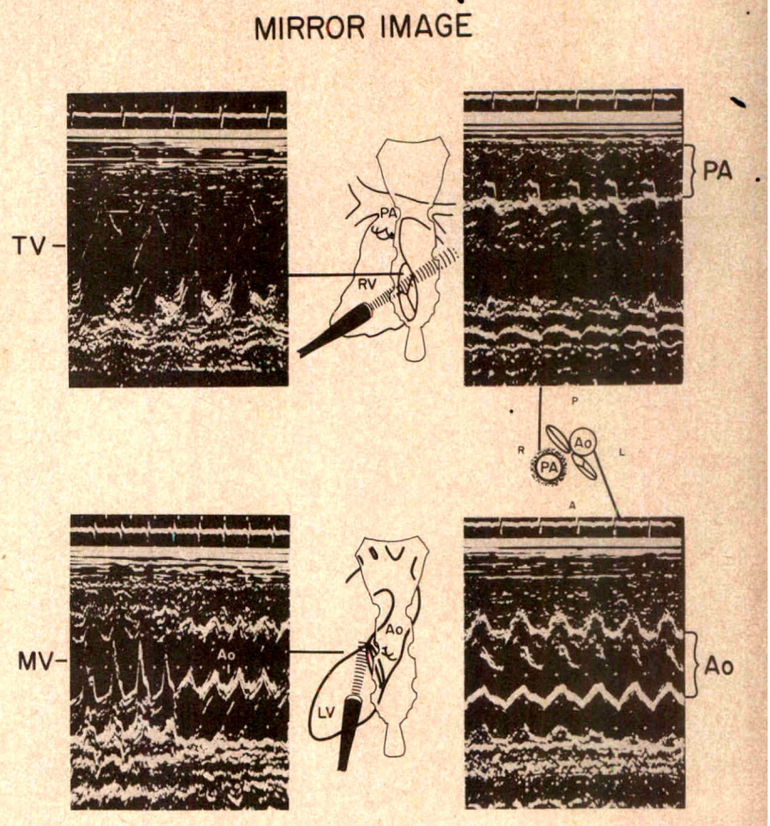

FIGURE 3. Case 5. Composite picture showing the transducer position for recording the mitral and tricuspid valves in a patient with mirror-image dextrocardia. The echograms show the relations of the cardiac structures. Abbreviations as in Figure 2.

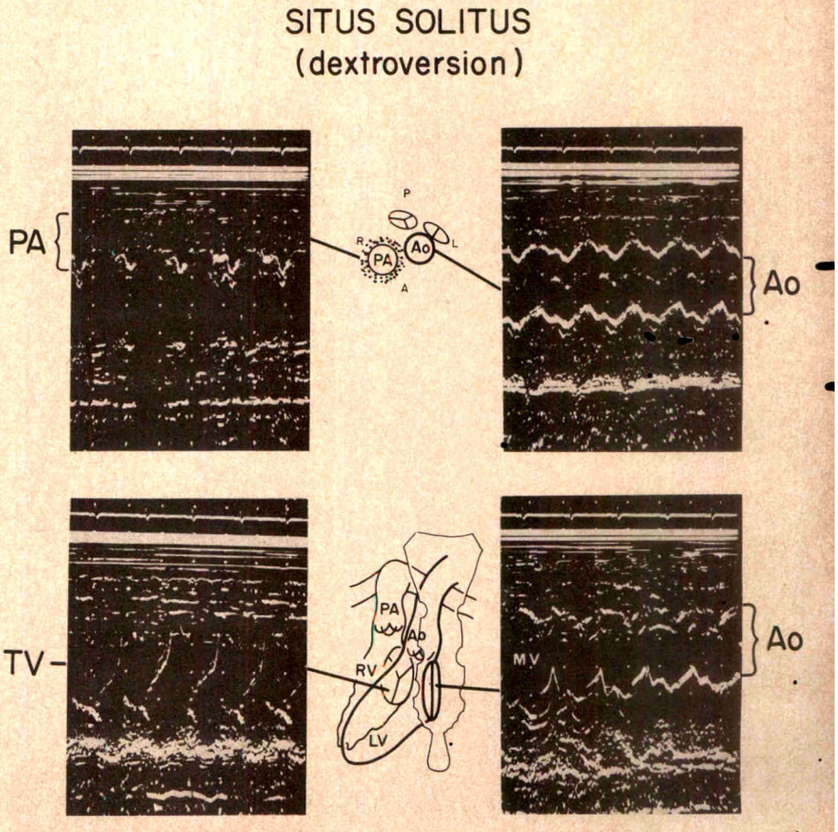

FIGURE 4. Case 8. Composite picture demonstrating the anatomic-echographic relations of the cardiac structures in a patient with isolated dextrocardia and normally related structures. Abbreviations as in Figure 2.

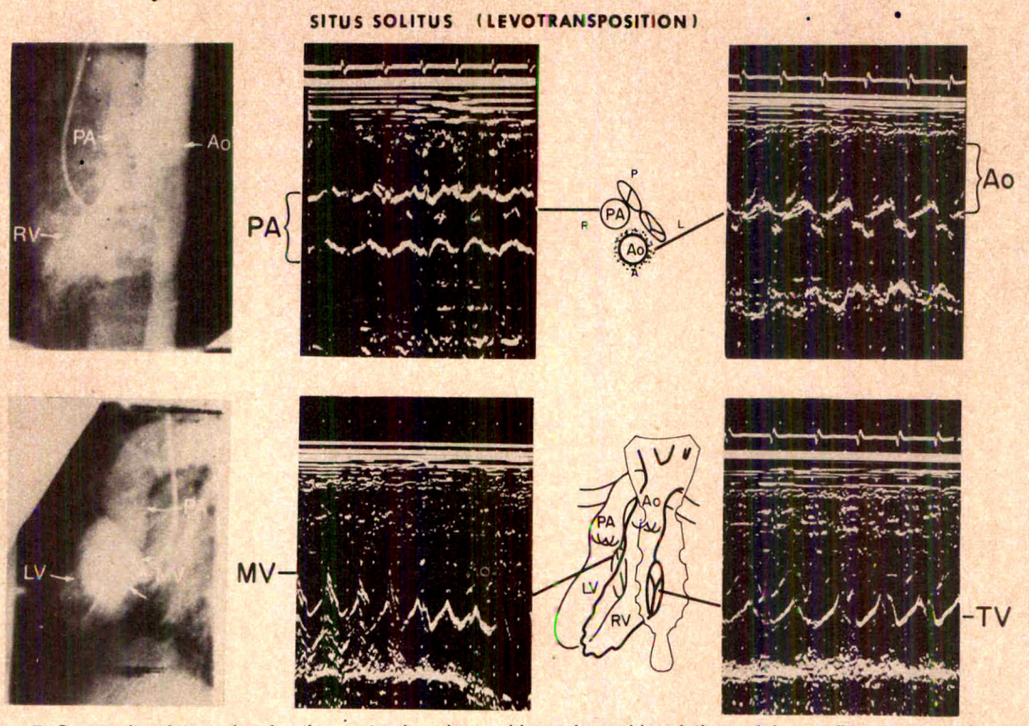

FIGURE 5. Case 7. Composite picture showing the anatomic-echographic-angiographic relations of the cardiac structures in a patient with isolated dextrocardia and ventricular inversion. The aortic root echo was obtained anteriorly and to the left. Abbreviations as in Figure 2.

and gastric air shadow in a patient with a normal atrial and visceral situs (solitus) and dextrocardia with levotransposition of the great vessels. The symmetrical appearance of the tracheobronchial tree of the patient shown in Figure 1B suggested bilateral left lungs, a lesion frequently associated with polysplenia and complex intracardiac anatomy.[10] This patient had a single ventricle with a common atrium.

Normal heart: Figure 2, obtained from a patient with normal situs and a normal heart, shows the sternal landmarks and transducer position in relation to the underlying structures. The echo of the anterior leaflet of the mitral valve was recorded posteriorly and to the left of the tricuspid valve and was in continuity with the aortic root. The pulmonary root was recorded anteriorly and to the left of the aortic root. Since the pulmonary root arose from an infundibulum, it was not continuous with an atrioventricular valve. Thus, the cardiac relations in this patient were normal.

Mirror-image dextrocardia: Figure 3 is from Patient 5, who had dextrocardia and visceral situs inversus (total situs inversus). As expected, the mitral valve echo was obtained to the right of and posterior to the tricuspid valve. The anterior root echo was recorded to the right of the posterior root echo. These findings suggested mirror-image dextrocardia. Clinically, the patient had a normal heart.

Isolated dextrocardia with normally related great vessels: Figure 4 is from Patient 8, who had isolated dextrocardia. From the right sternal border, the mitral valve echo was recorded to the left of and anterior to the tricuspid valve. The pulmonary arterial echo was obtained anteriorly and to the right of the aorta. These echographic findings, in conjunction with the plain chest roentgenogram, suggested that there was atrioventricular concordance with normally related great vessels, that is, dextroversion of the heart.

Isolated dextrocardia with levotransposition of great vessels: Figure 5 demonstrates the findings in Patient 7, who had isolated dextrocardia. In this patient, the mitral valve echo was recorded posteriorly and to the right of the tricuspid valve. The great vessel echo, in continuity with the atrioventricular valve, was obtained posteriorly and to the right, whereas the anterior great vessel was recorded to the left. These echographic findings, together with the plain roentgenogram, suggested atrioventricular discordancy with transposed great vessels in a patient with situs solitus. The angiograms confirmed the diagnosis of levotransposition of the great vessels. The aorta arose from a morphologic right ventricle and to the left of the pulmonary artery. The left ventricle gave rise to a pulmonary artery, which was in continuity with the mitral valve.

Situs inversus totalis with dextrotransposition: Figure 6 illustrates the findings in Patient 3, who had situs inversus totalis. The mitral valve echo was recorded to the right of the tricuspid valve. The great vessel, in continuity with the mitral valve, was recorded posteriorly and slightly to the right, whereas the anterior root echo was recorded to the left. These findings were compatible with the diagnosis of dextrotransposition of the great vessels in a patient with situs inversus.

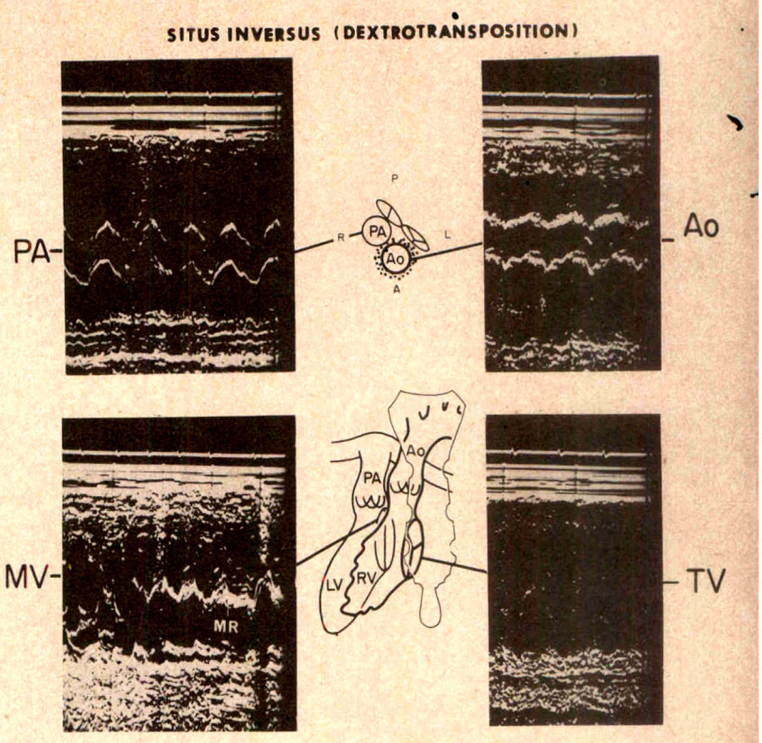

FIGURE 6. Case 3. This composite shows the anatomic-echographic relations of the cardiac structures in a patient with situs inversus and dextrotransposition. The left ventricle is on the right, but the anterior root echo was recorded to the left. MR = mitral ring; other abbreviations as in Figure 2.

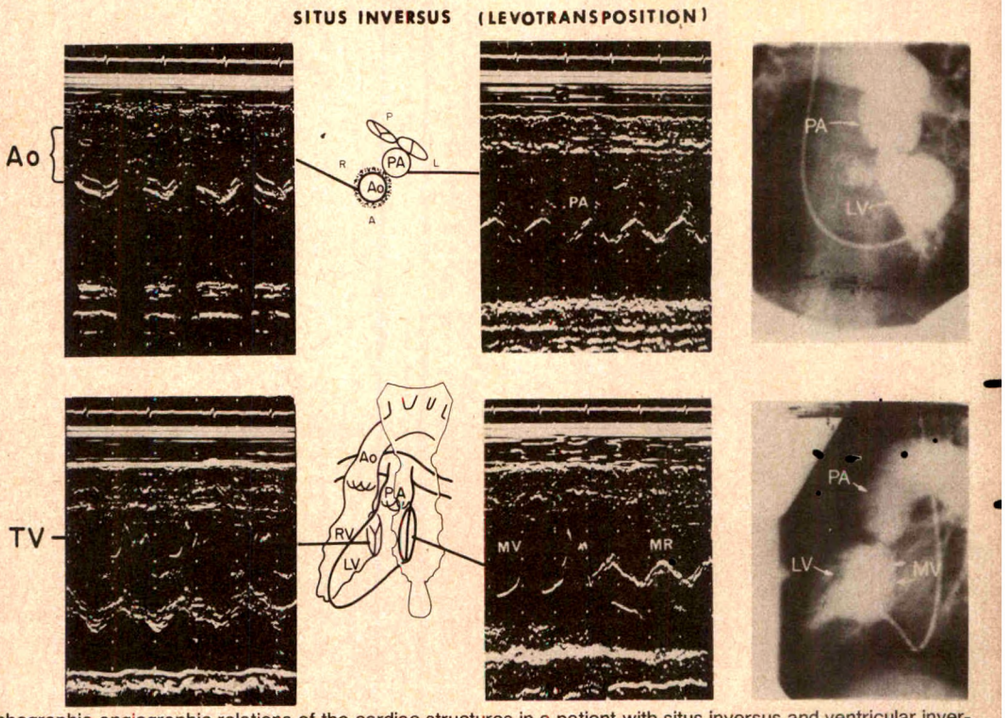

FIGURE 7. Case 10. Anatomic-echographic-angiographic relations of the cardiac structures in a patient with situs inversus and ventricular inversion. The anterior root echo was to the right, which suggested transposed great vessels. Angiography confirmed the diagnosis. Abbreviations as in Figures 2 and 6.

Situs inversus totalis and ventricular inversion: Figure 7 shows the findings of Patient 10, who had situs inversus totalis and ventricular inversion (levotransposition of the great vessels). The mitral valve echo was recorded to the left of the tricuspid valve and the anterior root echo was obtained to the right of the posterior root echo. These findings suggested levotransposition of the great vessels in a patient with situs inversus, and this diagnosis was confirmed by selective angiography.

Single ventricle: Figure 8 is from Patient 14, who had bilateral left lungs and situs inversus abdomi-

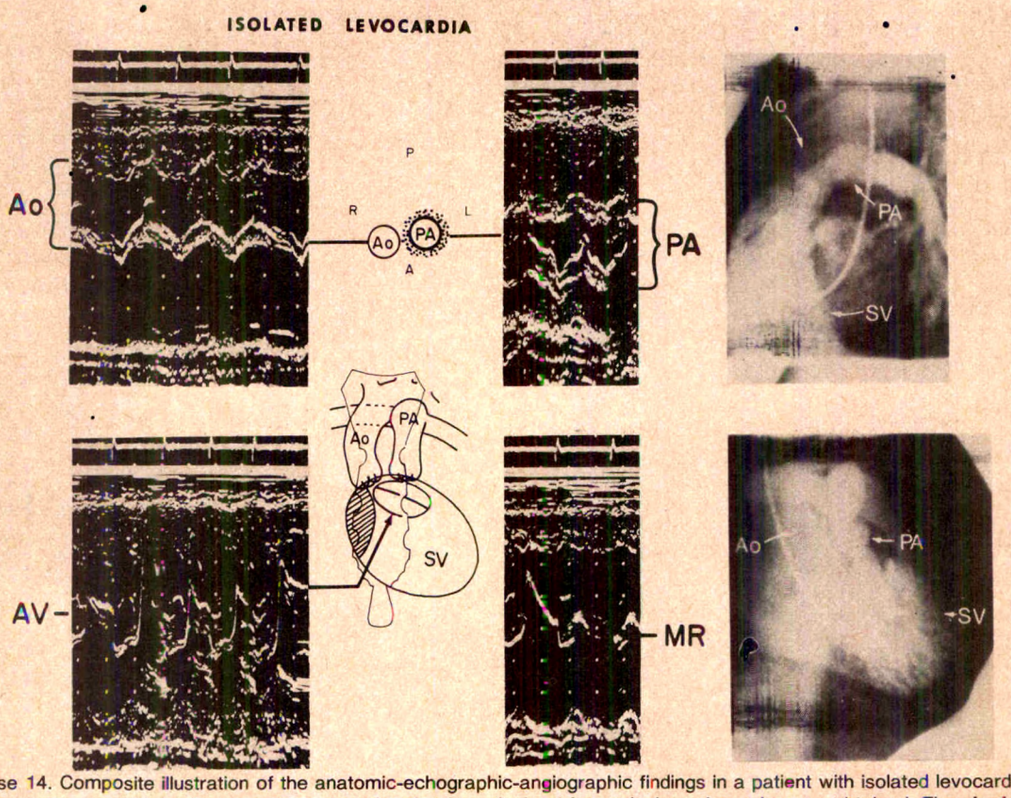

FIGURE 8. Case 14. Composite illustration of the anatomic-echographic-angiographic findings in a patient with isolated levocardia and indeterminate situs. A ventricular septal echo was not recorded and only a single atrioventricular valve echo was obtained. The **shaded area** represents the noninverted infundibulum. The anterior root echo was found to the right. Angiography confirmed the diagnosis of single ventricle and single atrium. A = anterior; Ao = aorta; AV = atrioventricular valve; L = left; MR = mitral ring; P = posterior; PA = pulmonary artery; R = right; SV = single ventricle.

nalis. A ventricular septal echo was not obtained and only a single atrioventricular valve echo was recorded. In addition, the anterior root was recorded to the right of the posterior root. These findings suggested single ventricle with dextrotransposition of the great vessels, and this diagnosis was confirmed by angiography.

Thirteen of the 15 patients studied by ultrasound underwent cardiac catheterization and angiography. The correct diagnosis was made from the echograms and plain chest roentgenograms alone in 11 of the 13 patients.

Discussion

Identification of the position of the left ventricle in patients with complex cardiac malformations is essential to correct diagnosis. This can be accomplished with the use of echocardiography because of the following anatomic features: (1) The atrioventricular valve follows the distal ventricular chamber,[8] and (2) with rare exception, the anterior leaflet of the mitral valve is in fibrous continuity with the semilunar valve arising from the morphologic left ventricle.[9] Thus, the characteristic echographic feature of the morphologic left ventricle is that its atrioventricular valve echo (mitral valve) is in continuity with a semilunar valve echo, whereas the tricuspid valve echo of the right ventricle is not in continuity with a semilunar valve echo.

Since ultrasound can determine the position of the left ventricle, the diagnosis of ventricular inversion can be made in patients with cardiac malposition. For example, in patients with isolated dextrocardia (situs solitus), the left ventricle should be recorded to the left (Fig. 4) unless there is ventricular inversion (Fig. 5). The converse is true in patients with total situs inversus. The left ventricle should be located on the right (Fig. 3) except in the presence of ventricular inversion (Fig. 7).

The arrangement of the great vessels can also be predicted by ultrasound. Although in our experience ultrasound cannot differentiate the aorta from the pulmonary artery, that information can be deduced if the relations of the root echoes and ventricles are known. For example, if a patient has situs inversus totalis (mirror-image dextrocardia) and the left ventricle is recorded to the right, then the expected position of the pulmonary artery is anterior and to the right (Fig. 3). However, if the anterior root echo is recorded either directly anterior to or to the left of the posterior root echo, then the great vessels are transposed and the anterior root is the aorta (Fig. 6).

Likewise, in a patient with isolated dextrocardia (visceral situs solitus) and a normally related heart,

the expected position of the pulmonary artery would be anterior and to the right (Fig. 4). However, if the left ventricle is to the right, implying ventricular inversion, then the anterior root is an aorta and the echo should be obtained to the left of the posterior root echo (Fig. 5).

Single ventricle can usually be detected by the absence of the ventricular septal echo and the presence of a single atrioventricular valve echo, which is in continuity with the posterior margin of the posterior root. In addition, the anterior margin of the posterior root echo may be difficult to record from the "mitral" valve position.

We conclude that with echocardiography and the knowledge of atrial situs, it is possible to define accurately important anatomic relations in a high percentage of patients with cardiac malposition. When catheterization is necessary, prior knowledge of the anatomic relations provided by diagnostic ultrasound will aid significantly in planning the study.

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Experimental Mitral Insufficiency (Bettelheim and Kauders)

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During the last 8 years the historical series in this Journal has included occasional articles on the experimental physiology of the heart valves.[1–5] The present contribution continues this line of interest and is devoted to the work of Karl Bettelheim and Felix Kauders entitled "*Experimentelle Untersuchungen über die kunstlich erzeugte Mitral-Insuffizienz und ihren Einfluss auf Kreislauf und Lunge*" (Experimental researches on artificially produced mitral insufficiency and its effect on the circulation and the lungs). The original essay was published in *Klinische und Experimentelle Studien aus dem Laboratorium von Professor Basch*, Berlin, 1891–96, Volume 1, pages 144–170.

Although the experiments of Bettelheim and Kauders were undertaken in order to explain clinical phenomena, and some experiments by their predecessors were performed for both clinical and physiologic purposes, the entire experimental series can be made to serve incidentally as a historical introduction to surgery of the heart valves.

Excerpts from Paper by Bettelheim and Kauders

In the present work it has been our endeavor to study by experimentation in animals the disturbances that are produced by deficiencies in valves and in this manner to gain more exact insight into them. By this method a stronger basis for clinical deduction can be created.

In general our predecessors in this field went to work in such a way as to produce insufficiency artificially, i.e. by instrumental damage. Since our work had to do with mitral insufficiency only, we shall mention from the pertinent literature only that which refers to this defect of valves . . . [The authors summarize the work of Klebs,* Rosenbach† and Francois-Franck‡.]

These experiments gave information only about the change which the arterial pressure, i.e., the work of the left ventricle, undergoes in consequence of artificially produced valvular defects, since only the carotid pressure was measured.

These measurements alone are the basis for the inferences which have been drawn from these experiments concerning the behavior of the right ventricle. The simultaneous behavior of both ventricles during artificial mitral insufficiency was tested for the first time by Stricker*; in an investigation on this subject he measured the pressure in the pulmonary artery at the same time as the pressure in the carotid . . . .

After all the experimental information that exists on mitral insufficiency, it cannot be said that our understanding of this circulatory disturbance can be regarded as closed. It rests in part on experiments which must be considered incomplete, since they afford information about arterial pressure only, and in part on experiments which are complete, since they consider the pressure in the pulmonary artery along with the behavior of the arterial pressure but contradict present clinical opinion. This contradiction expresses itself in the fact that in Stricker's experiments the elevation of pressure in the pulmonary artery—which clinical observation must infer from the demonstrable hypertrophy of the right heart and from the accentuation of the second pulmonic arterial sound—is lacking. In this connection it must be noted that Stricker himself in his experiment does not go against current clinical opinion. On the contrary, he mentions an experimental finding in favor of it. In a dog affected by organic mitral insufficiency a strikingly high pressure was observed in the pulmonary artery.

An investigation which has as its purpose to study the working of mitral insufficiency must concern itself above all with repeating Stricker's experiments concerning simultaneous measurement of arterial and pulmonary pressures in established mitral insufficiency. Such repetition seemed indicated not only with respect to the behavior of the pressure in the pulmonary arteries but also with respect to the [peripheral] arterial pressure. With respect to the latter also, the results, as we have already indicated, appear to be not unequivocal.

As has been stated, we attributed special importance to the measurement of the pressure in the pulmonary artery. For this reason we must deal first with trials in which half of the thorax was opened. However, once the thorax has been opened, and the heart—especially the left atrium—has become accessible, it appears more suitable to employ Stricker's method for the production of mitral insufficiency rather than the methods used previously by Klebs, Rosenbach and others. When the valve is torn or cut, the experiment is abandoned totally to chance. As we have convinced ourselves on a previous occasion, this alone determines

* Klebs, Ueber operative Verletzungen der Herzklappen und deren Folgen. Prager med. Wochenschr. 1876. No. II.

† Rosenbach, Ueber artificielle Herzklappenfehler. Schmiedeberg's Archiv. IX. Band.

‡ Francois-Franck, Comptes rendus des séances et memoires de la societe de biologie. 1882.

* Stricker, Lehrbuch 42. Vorl. S. 805.

This study was based on research assisted by Grant HL-10948 from the National Institutes of Health, Bethesda, Md.

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whether a large or a small defect is made in the valve. The size of the defect cannot be known during the experiment itself but can only be ascertained at autopsy. Moreover, by this method under the same conditions only one experiment can be undertaken in one animal. Through more extensive procedures in the same experiment it is always possible to make larger lesions in the valve but obviously this is not a repetition of an experiment under the same conditions. Further, by the procedure of injuring the valve a condition is introduced during the experiment which can by no means be regarded as to some extent constant. Therefore when experiments are conducted by this method, the results are very difficult to evaluate since the requirement of constancy of basic conditions is not met.

Up to a certain point this requirement is much more easily met when mitral insufficiency is produced by Stricker's method. The valves remain uninjured and the character of the communication between ventricle and atrium is conditioned only by the width of the cannula and the size of the window in it. Hence, when one and the same cannula is introduced through the ventricle into the atrium in different animals, approximately the same insufficiency is created. We say approximately the same, because complete equivalence could be produced only if one were able to use animals of the same size which had hearts of the same size.

The method mentioned has the additional advantage that several trials can be made in one and the same animal. For this purpose it is merely necessary to equip the cannula with an obturator. As long as this is in the cannula and obstructs the window, there is no insufficiency. When the obturator is pulled out and the window is left unobstructed, insufficiency is produced. That the degree of insufficiency is always the same needs no further proof. It might be possible for the window in the cannula to become blocked by blood clots during the experiment. In our experiments this did not happen, as we convinced ourselves afterward. It must be mentioned that this method produces not pure insufficiency but insufficiency combined with stenosis, since the cannula encroaches upon the space in the ostium.

In the experiment we went to work as follows. The animal was tied down, curarized and given artificial respiration. After preliminary preparation of the right carotid artery for subsequent attachment of a mercury manometer, the left chest was opened by resection of three or four ribs. A branch of the pulmonary artery was prepared. Both this and the carotid were equipped with a rounded cannula and connected to a mercury manometer. In order to determine the normal pressure relations, for a short time, a double kymographic tracing was made from the carotid and the pulmonary branch. Then the pericardium was opened. The left auricle was drawn forward and a sling of thread was placed around it. The auricle was then opened with a scissors. By way of the hole the von Basch cannula mentioned by Stricker and equipped with an obturator was thrust through the atrium into the ventricle. The sling was then drawn together and the part of the cannula that protruded from the auricle was fixed in place. After these preparations the recording of both pressures was resumed and was continued throughout the entire duration of the experiment . . . .

As might be expected, the resistance to drainage of the blood from the lung is greater when the obturator is removed and continuous communication is established between the left atrium and ventricle. This creates a condition which is equivalent to that caused by insufficiency of the mitral valve. In agreement with this supposition our experiments show that the ratio between arterial pressure and pressure in the pulmonary artery actually becomes still smaller than it is in the presence of stenosis . . . .

The establishment of an uninterrupted communication between the left ventricle and the left atrium, i.e., a communication that is not interrupted by systolic closure of the mitral valve—in other words, the artificial creation of mitral insufficiency—reduces the arterial pressure and raises the pressure in the left atrium and that in the pulmonary artery.*

This result of our experiments agrees completely with the concepts that we had formed with respect to circulatory occurrences in mitral insufficiency. However, our experiments warrant a more exact examination of the conditions that prevail during continued mitral insufficiency, since not general concepts and presuppositions but direct measurements—not merely of the arterial pressure but also of the pressure in the left atrium and pulmonary artery—provide the basis for our understanding . . . .

Table IV [not reproduced in the present excerpts] includes all those cases in which both the arterial pressure and the pressure in the pulmonary artery rise during the insufficiency. In this table it can be seen that, except in the case marked with an asterisk, the arterial pressure rose more. This relatively greater rise in the arterial pressure indicates a relative increase in the numerator compared with the denominator in our experiments on the circulation and justifies the opinion that the conditions for compensation, in the clinical sense, are to be sought not in the right heart but in the left . . . .

As can be seen, the results of our experiments are not favorable to the dominant opinion, namely that compensation in mitral stenosis depends on additional work of the right heart. Our results, on the contrary, support the opinion that conditions such as exist in the left heart—or, to express the matter in a more general way—conditions which arise in the greater circulation, can exert a favorable influence on the circulatory impairment which develops during mitral insufficiency.

Further experiments will be necessary in order to clarify the nature of these conditions . . . .

With respect to the theory of compensation and its impairment our experiments furnish the dictum that compensation can occur not only in the presence of high arterial pressure but also in the presence of low arterial pressure and that a fall in arterial pressure is not always equivalent to impairment of compensation.

Starting with the figures in our experiments we have defined the concepts of compensation and of impaired compensation in a manner differing from what is customary among clinicians. For us compensation is equivalent to an increase in the proportional figure and impaired compensation is a decrease in the proportion; despite this, what we understand by compensation does not differ in principle from that which the term commonly signifies. The clinician infers compensation when symptoms are lacking which indicates profound circulatory impairment, e.g., dyspnea, dropsy, edema, phenomena of stasis, etc. Compensation in our sense is not recognizable by the lack of symptoms, i.e., negatively, but positively through the demonstration of a larger proportional figure, which corresponds to more favorable circulatory conditions. Thus it can be seen that in the final result our concept of compensation coincides with

* As already stated, the elevation of the pressure in the pulmonary artery is expressed clinically, according to a general assumption, by accentuation of the second pulmonic heart sound. Since the elevation causes increased work by the right heart, in cases of long duration it must lead to hypertrophy. It is well known that this occurs.

that to which clinical observation leads at the bedside. The definition of impaired compensation which we have reached on the basis of our experimental figures is, as reflection reveals, basically identical with that to which clinical consideration leads. At the bedside one speaks of impaired concentration when symptoms appear which are referable to excessive filling of the lesser circulation and venous system; whereas we [experimenters] understand by impaired compensation a diminution of our proportional figure, due either to decline of the [peripheral] arterial pressure or to rise of the pressure in the pulmonary artery. That both of these occurrences give rise to the symptoms on which clinical observation establishes the diagnosis of impaired compensation, is quite intelligible.

We omit to add further clinical considerations to these results of our experiments. With respect to this, clinical research must teach us whether and to what extent the facts of clinical observation agree with the experiments and with the conclusions derived from them.

From the results of the hemodynamic experiments that we have reported above, it follows that during artificial mitral insufficiency the blood in the lungs flows under high pressure but low gradient, since during insufficiency not only the pressure in the pulmonary artery but also that in the left atrium is elevated. As can readily be seen, this causes severe overfilling of the pulmonary vessels. In this way the conditions arise which, according to the teaching of von Basch,* may lead to swelling of the lungs and finally also to rigidity of the lungs.

This made it necessary to ascertain by direct experiment whether in actual fact the lung becomes swollen and rigid in consequence of artificial mitral insufficiency. To repeat briefly, according to the teaching of von Basch swelling of the lungs is a consequence of widening of the alveoli due to increased pressure in the pulmonary capillaries. This widening must be followed by enlargement of the internal space in the lungs. In a larger series of experiments, carried out in this same laboratory by Dr. Grossman (p. 80) in which high pressure filling of the pulmonary vessels was induced by muscarine poisoning, choking, obstruction of the left atrium, squeezing of the left ventricle and compression of the aorta, enlargement of the internal space was demonstrated clearly. Thus, these trials show that swelling of the lungs arises after intense overfilling of the lungs with blood.† It was questionable whether the degree of overfilling produced in our experiments by means of artificial mitral insufficiency is sufficient to cause demonstrable swelling of the lungs or to cause increase in their internal space . . . .

The increased pulmonary volume, von Basch's "swelling of the lungs," can surely be demonstrated during insufficiency. As our experiments show, stiffness of the lungs—in mild grades only—can also develop as a consequence of mitral insufficiency. It follows, in agreement with the hemodynamic experiments, that the filling of the blood vessels of the lung that occurs during artificially produced mitral insufficiency does not occur under very high pressure. As is shown by the subsequently demonstrated enlargement of the internal space and of the external volume of the lungs, this pressure is able to widen the alveoli but it seldom leads to such pressure on the capillaries as affects the expansibility of the lung to the extent that severe rigidity develops. We wish to emphasize that this conclusion as to the influence of mitral insufficiency on the lung is of practical importance, since it throws new light on the tendency of the patient who has mitral insufficiency to develop dyspnea. According to our experiments the lungs of a cardiac patient of this kind must be abnormally large and they are, so to speak, in a condition similar to emphysema. Therefore they are less suitable for respiration than normal lungs. This diminished suitability of the lungs does not show itself at rest in cases of fresh but clearly demonstrable deficiencies of the heart; it first makes its appearance when the action of the heart is altered by even slight degrees of effort.

Finally we must point out that enlargement of the lungs in cases of cardiac deficiency has not escaped clinical observation. In the writings which Traube left behind we find the following passage in a note titled "Emphysematous Chest in Heart Patients": "Young persons affected with organic heart disease quite often have an abnormally voluminous and vaulted thorax, together with considerable increase in the volume of the lungs . . ." We must interpret this statement of Traube as signifying that the results of our experiments on animals have their analog in man.

Comment on Experiments of Bettelheim and Kauders

The authors state that their experiments were instituted for the deliberate purpose of throwing light on the clinical phenomena observed in valvular heart disease, specifically mitral insufficiency. They point out that some of the earlier investigators who had experimented on the valves had limited their observations to measurement of carotid arterial pressure, a procedure that could hardly yield information on the behavior of the right ventricle. Salomon Stricker, however, had measured simultaneously the pressures in the pulmonary and carotid arteries. Bettelheim and Kauders, pointing out certain inadequacies in Stricker's methods, resolved to repeat the investigation while observing the pressures in both the pulmonary artery and a peripheral artery.

Since, as previous investigators had admitted, lacerations of valves produced by the blind insertion of metallic sounds were difficult to control, Bettelheim and Kauders followed Stricker's clever method of producing mitral insufficiency by fixating a cannula in the atrioventricular orifice, thereby in effect joining the atrium to the ventricle. To vary conditions, they provided their cannula with an obturator. They remark that the cannula produced not pure mitral insufficiency but insufficiency complicated by stenosis, since the instrument occupied space in the atrioventricular orifice.

Kymographs were connected to both the carotid and pulmonary arteries and special attention was paid to the ratio between the two pressures. It was found that during continuous mitral insufficiency pressure in the carotid artery tended to be reduced and that in the pulmonary artery tended to be increased. When both pressures increased the former tended to increase more. From this the inference was drawn that in clinical cases of mitral insufficiency compensation depended more on the left ventricle

* von Basch: 1. Ueber eine Function des Capillardruckes in den Lungenalveolen. Wiener med. Blätter, 1887, no. 15.—2. Die cardiale Dyspnoe und das cardiale Asthma. Klinische Zeit- und Streitfragen. Wien 1887. S. Auch S. 49 u. 53.

† [Footnote deleted.]

than on the right. This conclusion was clearly recognized to run counter to dominant opinion. Further, it was concluded that compensation could exist in the presence of either an increased or decreased arterial pressure. This aspect of the investigation leads to a prolix discussion which it has been impossible to include in the foregoing excerpts. What is chiefly significant is that the problems of clinical disease constantly remained at the focus of the argument.

Editor's note: This is the 100th article on the history of medicine written by Dr. Jarcho for this Journal.

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Tachycardia-Dependent and Bradycardia-Dependent Mobitz Type II Atrioventricular Block Within the Bundle of His

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This report describes the occurrence in a young man of transient Mobitz type II and complete atrioventricular (A–V) block due to a lesion within the proximal portion of the His bundle probably caused by excessive alcohol intake. Initially A–V block was precipitated by tachycardia only but it subsequently became solely bradycardia-dependent before disappearing completely after a few days. Bundle of His electrograms demonstrated block above the site of recording of the His bundle potential.

The advent of His bundle electrocardiography has contributed greatly to our understanding of atrioventricular (A–V) conduction and has demonstrated that conduction block within the bundle of His may not be as rare as previously suspected.[1–8] In this report, we document interesting sequential changes in A–V conduction in a patient who exhibited transient second and third degree A–V block with a normal QRS complex. Bundle of His electrograms demonstrated block above the site of recording of the His bundle potential. Initially, A–V block was precipitated by tachycardia only but subsequently it became solely bradycardia-dependent (phase 4 block) before disappearing completely.

Case Report

A 27 year old man was admitted to the Genesee Hospital on April 26, 1972 because of several episodes of light-headedness during the preceding 24 hours. The patient had been in good health and took no medications, but he volunteered that he had consistently consumed very large quantities of whiskey every day for several weeks before admission in contrast to his usual intake of 12 to 15 cans of beer a week for several years. On examination, he was well nourished and afebrile. The pulse rate was 52/min and regular and blood pressure was 125/65 mm Hg. There were no signs of congestive heart failure, and no gallop sounds were audible. A very soft grade 1/6 short midsystolic murmur was heard along the left sternal edge associated with physiologic splitting of the second heart sound. No systolic clicks were detected.

Chest X-ray findings were normal. The initial electrocardiogram (Fig. 1) demonstrated sinus tachycardia (105/min) with complete A–V block and a junctional rhythm of 53/min. The QRS configuration, duration and mean frontal plane axis (+20°) were all normal. Hematologic studies, blood urea nitrogen and serum electrolytes were all within normal limits. Transient elevation of serum glutamic pyruvic transaminase levels occurred with a peak of 90 international units (normal 10 to 30 IU) in the absence of elevations of serum glutamic oxaloacetic transaminase, total and fractional lactic dehydrogenase and creatine phosphokinase levels. Serum alkaline phosphatase and bilirubin also remained within normal limits and bromsulfophthalein retention was 5 percent 45 minutes after intravenous injection of 5 mg/kg body weight. Despite the history of heavy alcohol intake, there was no clinical evidence of withdrawal symptoms. Immunologic studies (antistreptolysin O, heterophiles antibody, serum protein electrophoresis, immunoelectrophoresis, rheumatoid and antinuclear factors) and specimens for viral isolation and viral antibody titers in the acute and convalescent phases were unrevealing in the search for etiologic factors.

From the Division of Cardiology, Department of Medicine, the Genesee Hospital and the University of Rochester School of Medicine and Dentistry, Rochester, N. Y. This study was supported by a grant from the Genesee Valley Heart Association (Dr. Barold) and H. L. Grant 05500 (Dr. Goodfriend). Manuscript accepted August 9, 1973.

Address for reprints: S. Serge Barold, MB, the Genesee Hospital, 224 Alexander St., Rochester, N. Y. 14607.

Electrocardiographic Findings

A marked sinus arrhythmia was intermittently present throughout the patient's hospital stay and was noted when he was both awake and asleep. Continuous electrocardiographic monitoring documented the following sequential changes in A–V conduction. (1) *Day 1:* Complete A–V block occurred with a narrow QRS complex as seen in the initial electrocardiogram (Fig. 1), in which the sinus rate is 105/min and the junctional rate 53/min. (2) *Day 2:* There were intermittent periods of tachycardia-dependent Mobitz type II A–V block[9] with a narrow QRS complex and a P–R interval of 0.18 second (Fig. 2, A and B). At this time, complete A–V block occurred only with further acceleration of the sinus rate but not with long sinus cycles (Fig. 2, F and G). (3) *Day 3:* Periods of Mobitz type II and 2:1 A–V block occurred without apparent or measurable changes in sinus rate (Fig. 2, C and E). (4) *Days 4 to 6:* Frequent periods of bradycardia-dependent Mobitz type II and high degree A–V block were recorded during periods of sinus arrhythmia only when the P–P interval lengthened to a critical value in excess of 1,280 msec, as demonstrated in Figure 3 (compare Fig. 2, F and G). Prolonged periods of ventricular asystole were repeatedly observed during sleep (Fig. 3, B to F), and normal conduction was frequently restored by arousing the patient. During this phase, the patient consistently exhibited 1:1 A–V conduction (P–R interval 0.18 second) with short P–P intervals previously associated with tachycardia-dependent block. (5) Recovery and normal A–V conduction in the second week of hospitalization were followed by complete absence of any manifestation of heart block for a follow-up period of more than 1 year.

Throughout the hospital course, the patient was treated with propantheline bromide (Pro-banthine®), 15 mg orally every 6 hours, at the insistence of his private physician. After prolonged continuous monitoring revealed apparent complete recovery of A–V conduction, the patient was discharged without a pacemaker. He has abstained completely from alcohol and has remained asymptomatic. Follow-up studies during the past 14 months have included multiple Holter monitor (Avionics) electrocardiographic tape recordings that showed no evidence of recurrent conduction abnormalities. Repeated attempts to induce A–V block by applying pressure to the carotid sinus have failed.

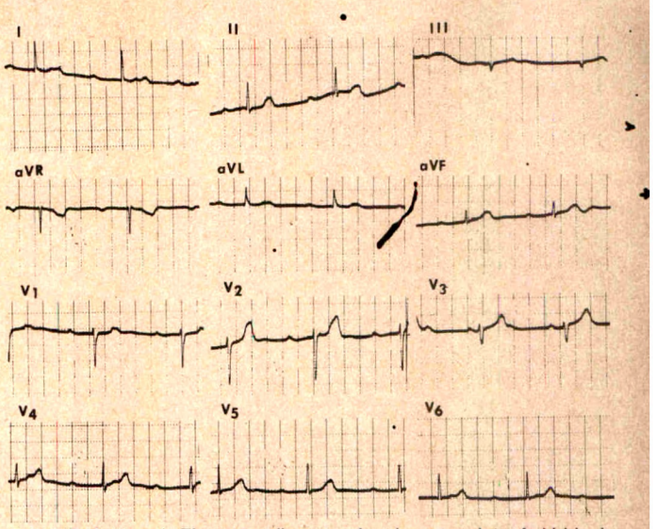

FIGURE 1. Day 1: Electrocardiogram showing complete A–V block with a sinus rate of 105/min and a junctional rate of 53/min.

Electrophysiologic Studies

On the second hospital day, His bundle electrograms were recorded by standard techniques using a no. 5F bipolar catheter with electrodes 1 cm apart. Filtered electrograms (40 to 500 Hz) were recorded on a multichannel oscilloscopic photographic recorder (DR12, Electronics for Medicine) simultaneously with surface leads I, aVF and V_1

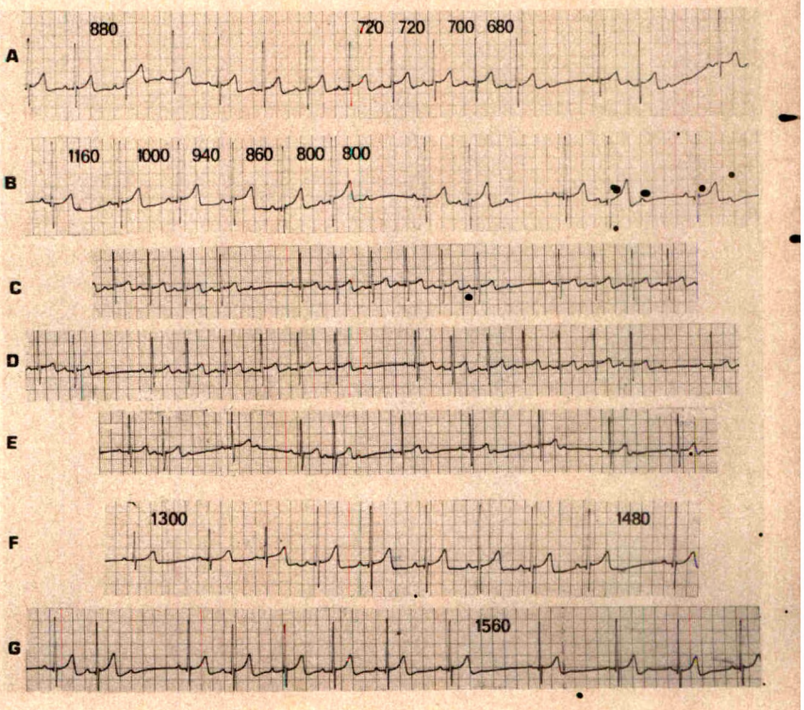

FIGURE 2. Strips **A and B** (Day 2) show tachycardia-dependent Mobitz type II A–V block. The P–R interval of 0.18 second remains constant before and after the nonconducted P waves. Strips **C to E** (Day 3) show periods of Mobitz type II and 2:1 A–V block without measurable changes in sinus rate. Similar recordings were obtained toward the end of the second day. Strips **F and G** (Day 2) show absence of A–V block when sinus arrhythmia causes marked bradycardia.

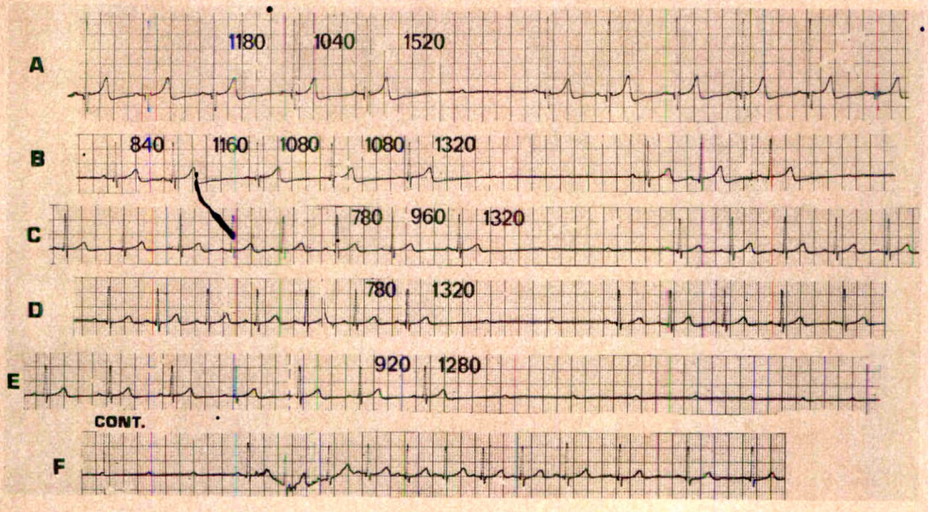

FIGURE 3. Days 4 to 6: Bradycardia-dependent A–V block. Strips **E and F** are continuous. Strip **A** shows Mobitz type II A–V block. Strips **B to F** show high degree A–V block only when the P–P interval lengthens to a critical value in excess of 1,280 msec. Note that the P–R interval (0.18 second before the dropped impulse or impulses) remains 0.18 second when A–V conduction resumes except in strip **B,** in which the P–R interval is a little longer because of an A–V junctional escape beat. Normal A–V conduction resumes at a P–P interval significantly shorter than 1,280 msec. The reason for this change is unclear but may be related to alterations in membrane responsiveness,[17] hypopolarization or repetitive concealed conduction and discharge of subsidiary pacemakers.

at paper speeds of 100 mm/sec. Intervals were measured according to the criteria of Narula et al.[3]

Figure 4, A and B, demonstrates Mobitz type II A–V block with narrow QRS complexes. The P–P interval ranges from 590 to 620 msec. The A–H time of 120 to 125 msec is slightly beyond the upper limit of normal (50 to 120 msec)[3] and is constant both before and after the blocked impulses. Duration of the His potential and the H–V interval of 40 msec are normal.[3] The absence of a His potential after the atrial deflection in nonconducted impulses localizes the block above the level of recording of the His potential and, therefore, within the A–V node or the proximal bundle of His. Figure 4C shows a segment of 2:1 A–V block. In each instance, no His bundle deflection follows the atrial potential of the nonconducted impulses. When complete A–V block occurs (Fig. 4D) the subsidiary focus appears to originate from the bundle of His as indicated by the constant occurrence of the His potential before a normally conducted QRS complex; the configurations of the His spike and the H–V interval (40 msec) remain identical compared with that of the conducted sinus impulses. Although the amplitude of the *A* wave varied throughout the recording period because of catheter movement and respiration, every conducted P wave (more than 200 were available for analysis) gave rise to a clearly visible His bundle spike with an amplitude that bore no relation to the size of the *A* wave. Therefore the consistent failure to record the His potential only after blocked *A* waves must be real and cannot be attributed to catheter movement.

Because the conduction pattern (Mobitz type II block) suggested a lesion within the bundle of His rather than within the A–V node, systematic exploration of various recording sites was carried out to search for "split" His potentials,[1,5] but none were found. Numerous attempts to pace the His bundle[10] were unsuccessful probably because of the strategic site of the lesion.

No junctional extrasystoles were noted during 6 days of continuous monitoring and no concealed His bundle extrasystoles were recorded during His bundle electrography, thereby excluding concealed extrasystoles as a potential cause of pseudo-Mobitz type II block.[8,11]

Validation of His bundle potentials has recently been the subject of lively debate.[5,12,13] We believe that in all likelihood the deflection labeled H represents His bundle depolarization rather than the right bundle (RB) potential for the following reasons: (1) Consistent recordings of a large triphasic H potential were achieved with similar H–V intervals (40 msec) upon repeated repositioning of the catheter. (2) The normal RB–V interval is less than 27 msec,[14,15] although right bundle branch disease cannot be excluded in this case. However, no terminal slurring or conduction delay was seen in lead V_1. (3) The recording of large *A* waves in the His bundle electrogram suggests the potential labeled H represents His bundle depolarization. Sizable atrial potentials are rarely seen when a large right bundle potential is recorded.[14–16]

Discussion

Bundle of His electrograms in our patient localized the site of block above the level of recording of the His potential. However, several features suggest more precise localization of the lesion within the proximal portion of the His bundle as opposed to the A–V node: (1) The P–R interval of 0.18 second remained constant and did not shorten after impulses were suddenly blocked or when stable 2:1 A–V block supervened. In contrast, when increased refractoriness causes A–V nodal block, either at constant or slightly changing P–P intervals, A–V conduction after a blocked impulse occurs with a shorter P–R interval. The P–R interval could remain constant when block occurs in the lowest part of the A–V node, but this situation must be rare clinically. (2) No Wenckebach cycles were observed during an extensive period of observation. (3) The occurrence of bradycardia-dependent block favors a lesion in which there are cells with potential automatic activity[17] (His-Purkinje system, as discussed later).

Mobitz type II A–V block: Our case clearly represents an example of type II A–V block according to the classification originally conceived by Mobitz.[9] Fifty years later, confusion still exists about the definition of Mobitz type II A–V block.[18] We believe that its use should be restricted to an electrocardiographic pattern characterized by failure of a *single* impulse to conduct to the ventricles, in the absence of antecedent progressive lengthening of the P–R intervals, which may be normal or prolonged.[7,19–21] These P–R

intervals remain constant before and *after* the blocked impulse,[8,20–22] as implied by Mobitz,[9] who indicated in his diagrams that the R–R interval encompassing the blocked impulse was twice the basic cycle length.

Previous studies have demonstrated a strong correlation between Mobitz type II A–V block with His-Purkinje system (infranodal) lesions,[3,8,23–26] but this pattern has not been established conclusively as arising within the A–V node in experimental animals or man. Recent reports have claimed that Mobitz type II block can occur proximal to the His bundle during constant or slight variations in P–P intervals,[8,27–32] but atypical type I sequences cannot be excluded in most of those reports[28–32] because the initially prolonged P–R (or A–H) interval shortened after the dropped impulse. Narula[8] recently reported the sudden occurrence of high degree A–V block (which he called Mobitz type II block) without preceding prolongation of the P–R interval in a case in which the block appeared to be above the site of recording of the H potential. However, according to the concepts of Mobitz type II block cited, only the case of Langendorf et al.[27] and the present example represent Mobitz type II A–V block with a narrow QRS in which the block is localized above the site of recording of the His potential.

Bradycardia-dependent A–V block: Our patient exhibited bradycardia-dependent A–V block presumably caused by enhanced automaticity within the His-Purkinje system[17] (phase 4 block). Many examples of bradycardia-dependent bundle branch and, more recently, fascicular blocks have been described.[33–38] Bradycardia-dependent A–V block seems to be less common but was reported in 1971 by Coumel et al.,[36] who also identified other reported cases, and more recently by Rosenbaum et al.[39] There are two types of bradycardia-dependent A–V block[36,39]: (1) permanent or stable bundle branch block associated with bradycardia-dependent block in the contralateral bundle, which result in failure of A–V conduction at critically slow rates; and (2) block proximal to the bifurcation of the His bundle associated with a narrow QRS complex, by far the rarest form.[39] Both forms of block may be paroxysmal and undetected unless spontaneous or vagally induced bradycardia elicits A–V block, or spontaneous atrial or ventricular extrasystoles precipitate block by producing relatively long postextrasystolic pauses.[39,40] In this context, atrial extrasystoles or ventricular escape beats with critical timing may also terminate A–V block and restore 1:1 A–V conduction.[39,40]

Phase 4 depolarization seems the most likely cause for bradycardia-dependent block,[17] and there are several arguments against a vagal origin in our patient: (1) The relation between periods of sinus slowing and A–V block particularly during sleep makes it unlikely that surges of vagal tone were a primary mechanism. (2) P–R intervals remained constant and did not prolong with slowing of the sinus rate, and no Wenckebach cycles were observed. Both points favor the absence of vagal influence upon A–V nodal conduction. (3) Recent microelectrode studies have demonstrated that acetylcholine, because it depresses the slope of phase 4 depolarization in the His bundle and right bundle branch of the dog, may permit conduction to proceed more rapidly.[41] Consequently, vagal stimulation might be expected to enhance rather than to slow conduction in patients with phase 4 block. The role of propantheline in determining the sequence of events in our patient cannot be assessed. The concept of phase 4 depolarization thus provides support for the hypothesis of block within the proximal bundle of His rather than within the A–V node.

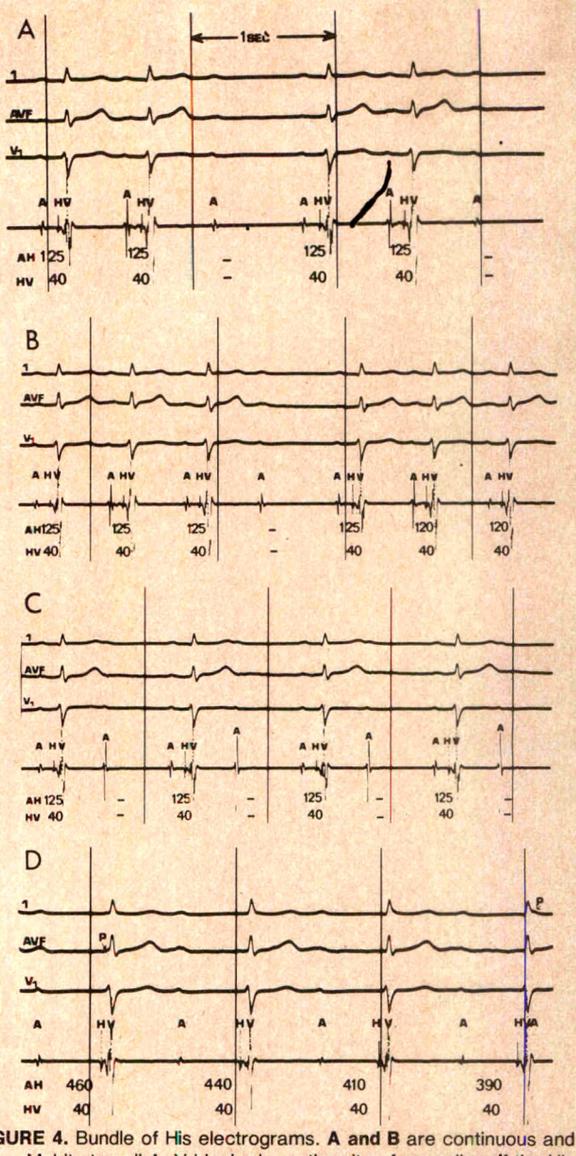

FIGURE 4. Bundle of His electrograms. **A and B** are continuous and show Mobitz type II A–V block above the site of recording of the His potential when the P–P interval measures 590 to 620 msec. **C** shows 2:1 A–V block when the P–P interval shortens to 530 msec. Note that the A–H interval of conducted beats is identical to the A–H intervals in **A and B. D** shows complete A–V block when the P–P interval shortens to 490 msec. No His spikes follow the *A* waves. Time lines = 1 second.

No specialized cells capable of spontaneous depolarization have yet been identified within the A–V node (at least in experimental animals) except for the transitional nodal-His (NH) region which has physiologic and anatomic properties intermediate between those of the A–V node and the bundle of His.[42] It would therefore be highly improbable for phase 4 bradycardia-dependent block to arise within the body of the A–V node in man.

Some cases of bradycardia-dependent conduction block have demonstrated both phase 3- (prolonged recovery)[43] and phase 4-related block either concurrently or sequentially in the same patient,[34,37–39,44] and El-Sherif et al.[38] recently succeeded in producing transient tachycardia- and bradycardia-dependent block in the right and left bundle branches and the His bundle of dogs after ligation of the anterior septal artery.

Etiology: We cannot exclude congenital A–V block as a cause, but the recent work of Ettinger et al.[45] suggests that alcohol might be important. These workers demonstrated that chronic ethanol feeding of well nourished dogs may result in prolongation of the H–Q interval and QRS complex and accumulation of a mucopolysaccharide-like material in the interstitium and dilatation of the sarcoplasmic reticulum, as observed in electron microscopic studies, in the absence of significant ventricular hypertrophy. Several of their animals died suddenly and unexpectedly, thus suggesting a possible relation to conduction abnormalities and arrhythmias. Conduction disturbances including A–V block and bundle branch block have frequently been observed in alcoholics.[46] In view of the high level of alcohol consumption and the conduction block that regressed with abstinence, ethanol must be considered an intriguing possibility for A–V block in our patient.

Bradycardia-dependent A–V block might be more common than realized and should be considered in the electrophysiologic investigation of syncope of possible cardiac origin. Interventions such as vagal maneuvers or the production of electrically induced premature atrial and ventricular beats may unmask bradycardia-dependent block.[36,39,40] The evanescent and apparently reversible clinical course of our patient suggests that the use of permanent pacing in phase 4 A–V block, particularly in young patients with a narrow QRS complex, should be considered only after an extended period of observation has excluded a potentially reversible lesion. The recent work of El-Sherif et al.[38] tends to support this view. Further follow-up studies of our patient will be required to determine whether our therapeutic decision was correct.

Acknowledgment

We are indebted to Dr. George Lovell for referring the patient to us and for his encouragement and support.

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Mitral and Tricuspid Lesions Associated with Polypoid Atrial Tumors, Including Myxoma

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The related atrioventricular valves in 11 instances of polypoid atrial tumors were examined grossly and histologically. Nine of the tumors involved the left atrium and, of these, seven were myxomas. The two right atrial tumors were myxomas.

Histologically evident lesions of the mitral valve were present in seven of the nine left atrial tumors. The most common change consisted of fibrous thickening of the endocardium in the angle between the left atrium and posterior mitral leaflet and fibrous thickening of the atrial surfaces of the leaflet. Less common changes were a fibrous thickening of the chordae and of the left ventricular mural endocardium in relation to chordae inserting into the posterior leaflet. The changes described were also evident at gross examination in two of the nine cases with left atrial tumors.

In the two cases of right atrial myxoma, both showed fibrous thickening of the atrial surfaces of the tricuspid leaflets; one also exhibited fibrous thickening of the right ventricular endocardium beneath the septal leaflet of the tricuspid valve.

The lesions described are considered responses to the effects of friction by the tumor upon the surfaces involved. It is significant that grossly evident lesions may evolve from this rubbing action.

Classically, left atrial myxoma is a condition associated with a normal mitral valve. Yet recent reviews have indicated that both structural and hemodynamic abnormalities of the mitral valve may be associated with this tumor.[1–6] The exact nature of the structural changes in the valve has not been described. Pilot studies by us have suggested that the mitral valvular lesions are responses to friction upon the valve by the characteristically polypoid atrial myxoma. Therefore, we undertook a study of the atrioventricular valves in hearts with several types of polypoid atrial tumors.

Case Material

Eleven specimens of hearts with polypoid tumors were available for restudy. These included nine examples of left atrial tumors — seven myxomas, one mesenchymoma and one recurrent myxosarcoma. Two specimens with right atrial polypoid tumors, each a myxoma, were also studied. The essentials of the 11 cases studied are summarized in Table I. Except for one child, aged 13 years, with a left atrial myxoma, the patients were adults ranging in age from 21 to 87 years.

Surgical excision of the primary tumor had been performed in two of the cases, a left atrial myxoma in one (Case 5) and left atrial myxosarcoma in the other (Case 9). Autopsy in both cases revealed recurrent tumor. In Case 5, the patient died of intestinal carcinoma 4 years after excision of the left atrial myxoma. The recurrent tumor was represented by a narrow, relatively long strand attached to the atrial septum (Fig. 1*a*). The size of the tumor indicated in Table I for this case is that of the surgically excised tumor; for the patient with recurrent myxosarcoma of the left atrium the size of the recurrent tumor is indicated.

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The tumors ranged in size from 2.5 by 2 to 11 by 4 cm (Fig. 1,*b* and *c*). In four the largest dimension was 4.0 cm or less; in seven the greatest dimension of the tumors ranged from 5.0 to 11.0 cm.

Except for the patients with the smaller tumors, deaths were usually attributed to the presence of the polypoid tumor. Congestive heart failure and sudden death were common manifestations of the tumor; in patients with the smaller tumors heart failure and sudden death appeared as incidental findings and were unrelated to the tumor. In one case previously reported,[7] a large right atrial myxoma was associated with diabetic Kimmelstiel-Wilson disease (Case 11) (Fig. 1*d*).

For each of the 11 hearts, standard gross examination was performed with particular emphasis upon the nature, location and size of the tumor as well as the condition of the atrioventricular valve homolateral with the tumor. Each of the valves involved was also examined histologically.

Samples for histologic study of the atrioventricular valves were taken as follows. For the mitral valve, a section was taken of its posterior leaflet, the related chordae tendineae and left atrial and ventricular walls. Sections of the tricuspid valve were taken through two zones, the septal and the anterior leaflets, each including the related right atrial and ventricular walls and chordae tendineae. For each sample, a slide was stained with hematoxylin-eosin and another with Lawson's elastic tissue counterstained with the van Gieson's connective tissue stain.

TABLE I
Summary of Data in 11 Cases Studied

Case no.	Age (yr) & Sex	Tumor Size (cm)	Histologic Lesions of Related A–V Valve
	Myxoma of Left Atrium		
1	59M	2.5 × 2	0
2	68F	2.5 × 2.5	+
3	42F	4 × 3	+
4	87F	4 × 3.5	+*
5	68M	5 × 5	+
6	42M	6 × 6	+
7	13F	11 × 4	0
	Mesenchymoma		
8	26F	6 × 4	+
	Recurrent Myxosarcoma		
9	21F	6 × 5	+*
	Myxoma of Right Atrium		
10	Adult(?)	3 × 2	+
11	61F	10 × 5	+

* Gross lesions also present.

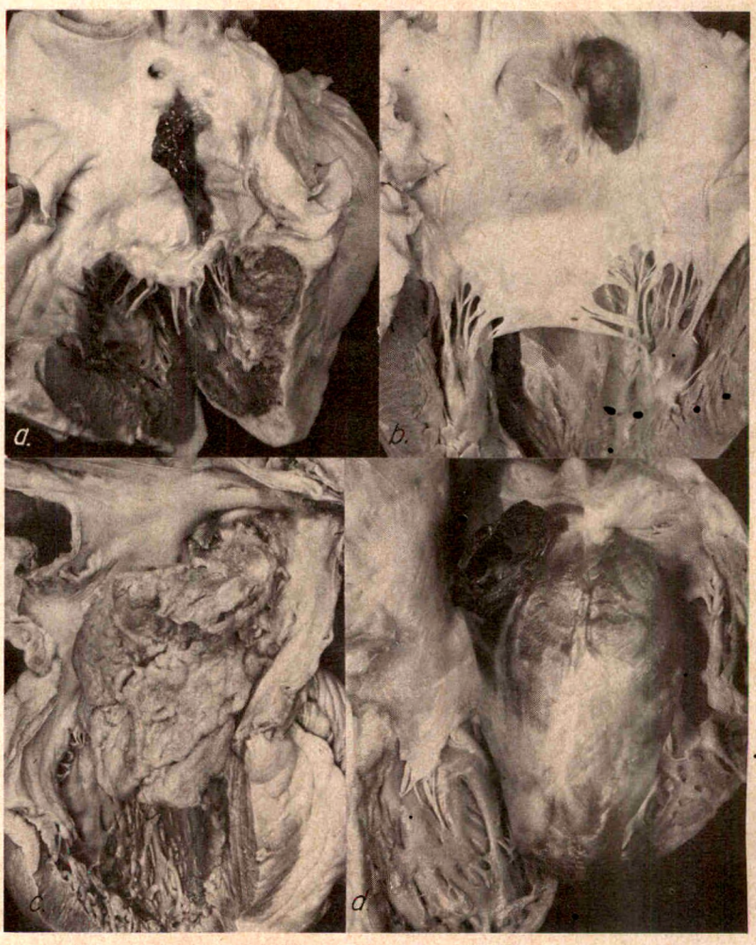

FIGURE 1. a, Case 5. Recurrent left atrial myxoma 4 years after excision of the primary tumor. The recurrent tumor is represented by a cylindrical gelatinous strand attached to the atrial septum. **b,** Case 1. The smallest left atrial myxoma in the series. No lesions of the mitral valve were present histologically. **c,** Case 7. The largest left atrial tumor in the series, from a 13 year old girl, showing a myxoma attached to the atrial septum. The tumor protrudes through the mitral valve and presents in the left ventricle. The mitral valve was devoid of lesions. **d,** Case 11. The larger of the two right atrial myxomas. The tumor is attached by a pedicle to the atrial wall and extends through the tricuspid orifice into the right ventricle.

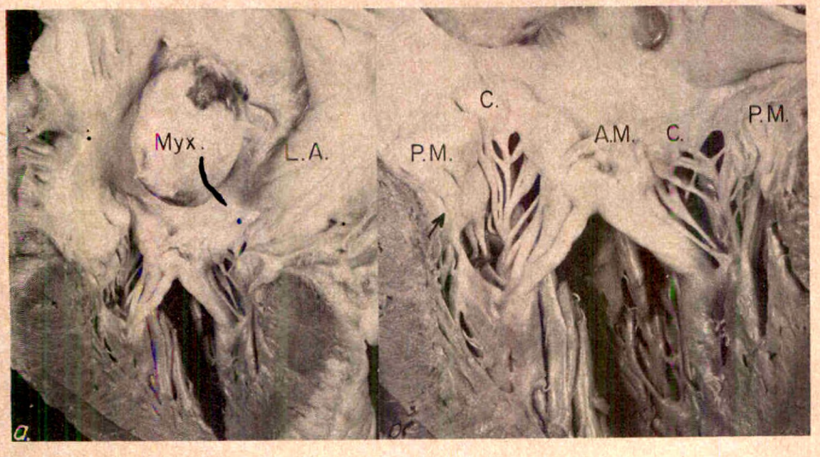

FIGURE 2. Case 4. Calcified left atrial myxoma associated with fibrosis of mitral valve. **a,** polypoid myxoma (Myx.) is attached to septal wall of the left atrium (L.A.). The mitral valve is abnormal. **b,** close-up view of mitral valve showing marked fibrosis of line of closure of anterior leaflet (A.M.) and of central chordae. There is sparing of the commissures (C.) and commissural chordae. The posterior mitral (P.M.) leaflet is fibrotic; its chordae are entrapped in fibrous tissue **(arrow)** of the related left ventricular wall.

Results

Gross Examination

Grossly, the semilunar valves were normal in each case as was the atrioventricular valve contralateral to the side of the atrial tumor. Gross abnormalities were noted in the mitral valve in one case with a calcified left atrial myxoma (Case 4) and another with left atrial recurrent myxosarcoma (Case 9). The more severe changes, fibrosis of the leaflets without commissural fusion, occurred in the former case. The chordae related to the commissures were relatively thin; the remaining chordae were thickened with fibrous tissue and interadherent. The left ventricular mural endocardium related to the chordae of the posterior leaflet was thickened with engagement of related chordae in the mural fibrous tissue (Fig. 2). The second instance with gross changes involved the case of recurrent polypoid left atrial myxosarcoma (Case 9).* The abnormalities of the mitral valve, although qualitatively like those in Case 4, were less severe and there was lack of left ventricular mural fibrosis (Fig. 3).

* The details related to recurrence of the tumor in this case are being reported elsewhere.[8]

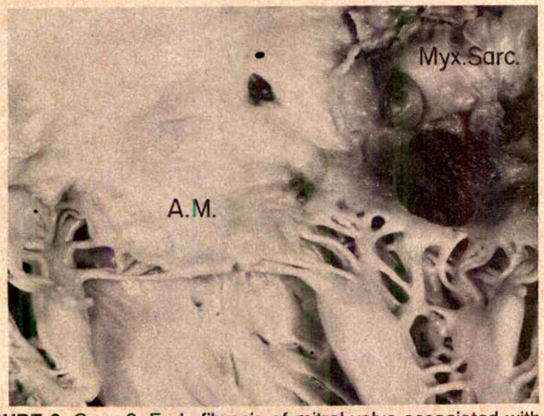

FIGURE 3. Case 9. Early fibrosis of mitral valve associated with pedunculated myxosarcoma (Myx.Sarc.) of left atrium. Diffuse thickening of the anterior mitral leaflet (A.M.) and chordae is evident.

Histologic Examination

In describing the results of histologic examination, we will consider the mitral valve first, then the tricuspid valve. None of the cases demonstrated abnormality of the myocardium except for invasion by tumor in the case of recurrent myxosarcoma.

Mitral valve: The following is a consideration of the mitral valve in nine cases of polypoid tumors involving the left atrium. The progressive disease leading to grossly visible abnormalities may be understood from changes observed in cases without grossly evident lesions. Some histologic abnormalities were noted in seven of the nine mitral valves studied; the two cases without lesions were examples of left atrial myxoma. When lesions were present, certain specific areas were involved (Fig. 4 and 5). The first of these areas was the endocardium in the angle between the posterior mitral leaflet and the left atrial wall. Six of the seven cases with lesions of the mitral valve noted histologically showed such a localization. The characteristic change was collagenous and elastic tissue thickening of the endocardium. Another common site for involvement was the atrial aspect of the valvular leaflets, seen in five of the seven cases. Surface fibrous thickening of chordae was observed in two cases and one, that with the more severe gross changes, showed fibrous thickening of the left ventricular mural endocardium in relation to chordae that attached to the posterior mitral leaflet (Fig. 5*b*). In this case, chordae were adherent to the mural fibrous tissue. In exceptional situations fibrous thickening of the left atrial wall was noted lying above the angle with the mitral valve.

The pathogenesis of the fibrous lesions described could be explained by observations among the several cases (Fig. 6). The first process appeared to be deposition of fibrin upon the endocardial surface. This was followed by fibroblastic proliferation and, finally, by maturation of the connective tissue with formation of elastic tissue.

Tricuspid valve: Neither of the two cases with right atrial myxoma showed lesions upon gross examination, but each showed histologic abnormalities. In each, there was fibrous thickening of the atrial sur-

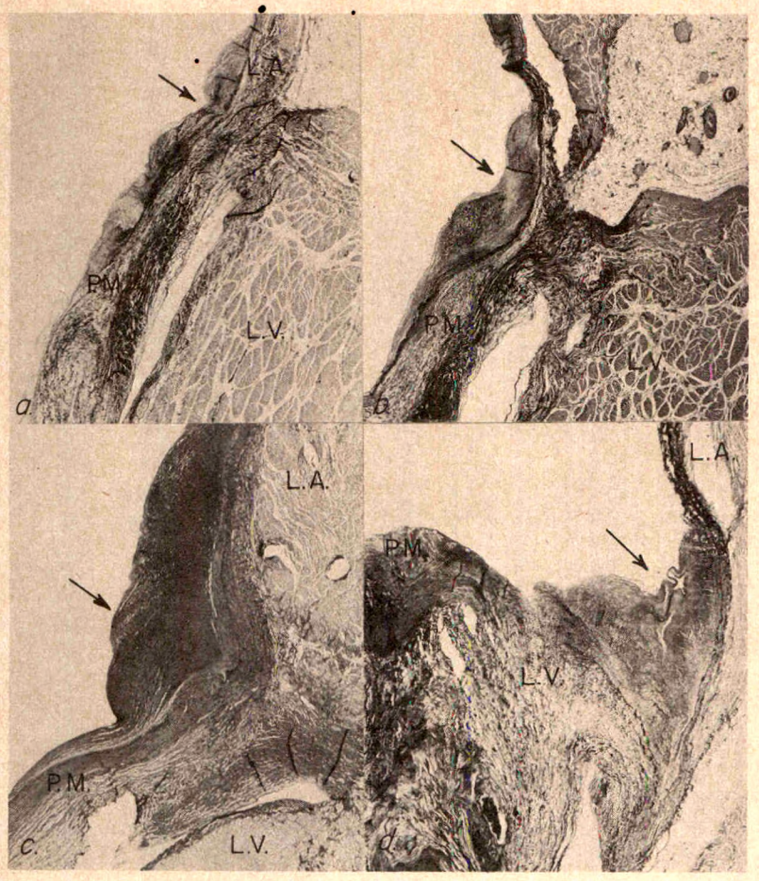

FIGURE 4. Photomicrographs of the base of the posterior mitral leaflet (P.M.), the base of the left ventricle (L.V.) and the angle **(arrow)** between the posterior mitral leaflet and the atrial wall (L.A.). **a,** Case 3. Fibrosis of the atrial surface of the valve leaflet and angle. **b,** Case 6. Slightly more severe fibrosis at angle. **c,** Case 5. Heavier and densely organized fibrosis. **d,** Case 4 (from case shown in Figure 2). Fibrosis at the angle between the leaflet and left atrial wall. All elastic tissue stain. × 12, reduced by 27 percent.

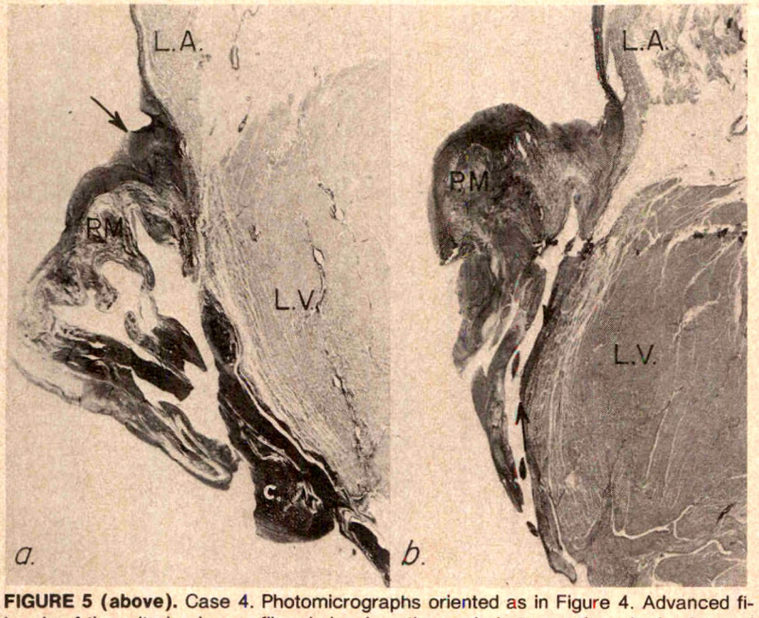

FIGURE 5 (above). Case 4. Photomicrographs oriented as in Figure 4. Advanced fibrosis of the mitral valve. **a,** fibrosis involves the angle between the mitral valve and left atrium as well as atrial and ventricular surfaces of leaflet and surfaces of chordae (c.). Elastic tissue stain × 2.5, reduced by 20 percent. **b,** additional changes include fibrous thickening (between vertical arrows) of left ventricular mural endocardium. Elastic tissue stain × 3.7 reduced by 20 percent.

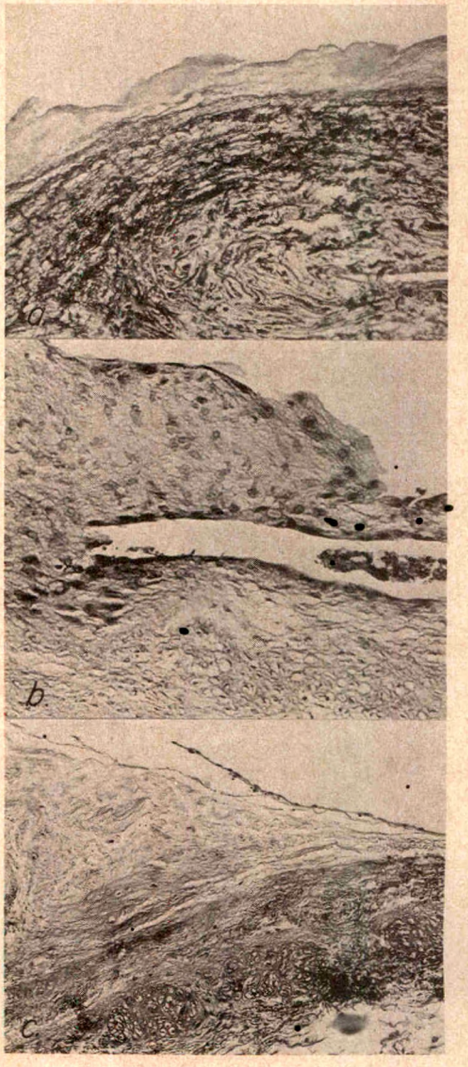

FIGURE 6 (right). Histogenesis of fibrous lesions. **a,** fibrinous deposit upon surfaces of valve (upper part of illustration). Elastic tissue stain × 47. **b,** fibrous proliferation. Hematoxylin-eosin × 50. **c,** collagenous formation. Elastic tissue stain × 50. All reduced by 16 percent.

faces of the leaflets. Additionally, in one (Case 11), there was fibrous thickening of the right ventricular mural endocardium beneath the septal leaflet (Fig. 7).

Comment

In reported cases[9,10] describing mitral valve disease in association with left atrial myxoma, the mitral disease has been considered rheumatic in origin. This assumption might be used to support the old view that left atrial myxomas are actually thrombi, a hypothesis that favors the mitral disease as primary and the "atrial myxoma" as a secondary thrombus. However, current evidence strongly supports the view that atrial myxoma is an entity different from a thrombus.[11] If one accepts the atrial myxoma as a separate entity and the mitral disease as rheumatic in origin, one is faced with coincidental unrelated conditions.

Nature of the mitral and tricuspid valve lesions: Our studies support a different concept, namely, that the mitral lesions are secondary to the traumatic effects of the tumor. We believe these lesions to be "friction lesions," that is, a reaction to rubbing of tissues by the atrial polypoid tumor. Highlights of our observations supporting this concept are: (1) None of the cases in our series showed evidence of Aschoff bodies, either healed or acute; (2) the peculiar pattern of developing fibrosis in these cases, particularly at the angle between the mitral valve and left atrial wall, is consistent with a reaction to friction by the tumor (rheumatic lesions do not possess this peculiar localization) (Fig. 8); (3) the gross anatomic features are characterized by absence of commissural fusion with remarkable preservation of the commissures and related chordae (the most severe changes were present in the mid-portions of the leaflets, whereas in rheumatic mitral disease commissural lesions are prominent); and (4) lesions of the tricuspid valve in instances of right atrial polypoid tumor are qualitatively like those of the mitral valve when a polypoid tumor is present in the left atrium.

The lesions described, which are considered friction lesions, should be added to other endocardial friction lesions that have been described from our laboratory. These are (1) lesions of the right ventricular endocardium in relation to chordae tendineae of the septal leaflet of the tricuspid valve in instances of left ventricular hypertrophy,[12] and (2) lesions of the left ventricular endocardium in relation to chordae tendineae of the posterior mitral leaflet in cases with hooding of the mitral valve.[13]

Explanation for absence of mitral valve lesion in two cases: Of the two left atrial tumors without mitral valve lesions, one tumor was the smallest in the series (Case 1), and the other the largest (Case 7). One may explain the absence of lesions in Case 1 on the basis of the small size of the tumor, which may not have extended to the level of the mitral valve. Absence of lesions in the case with the largest tumor might be explained by the soft gelatinous consistency of that tumor. It is of interest and in support of our view that the most severe lesions were observed in the one case with a calcified myxoma (Case 4).

Others[6] have mentioned the traumatic effects of atrial myxoma on the mitral and tricuspid valves, but a systematic study of pathologic changes in these valves has not been made. Mitral insufficiency associated with atrial myxoma has been abolished by surgical plication of the valve leaflet.[3,4,9] The cases in the present series did not include an example of mitral or tricuspid incompetence although such a phenomenon is recognized as a possibility.

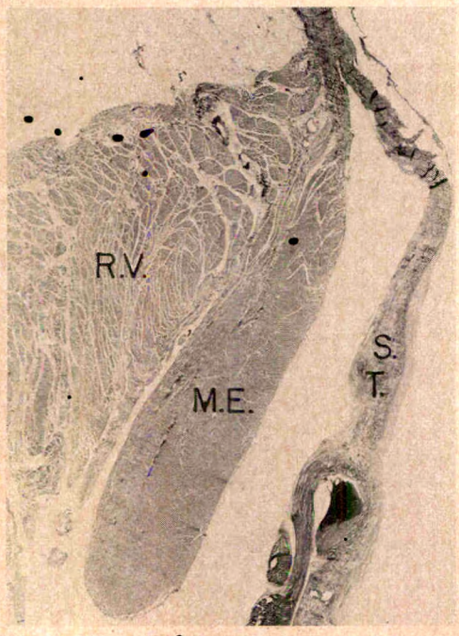

FIGURE 7 (left). Case 11 (from case illustrated in Figure 1*d*). Photomicrograph of septal tricuspid leaflet (S.T.) and related right ventricular wall (R.V.). Mural endocardium (M.E.) of the latter is thickened. Elastic tissue stain × 6.7.

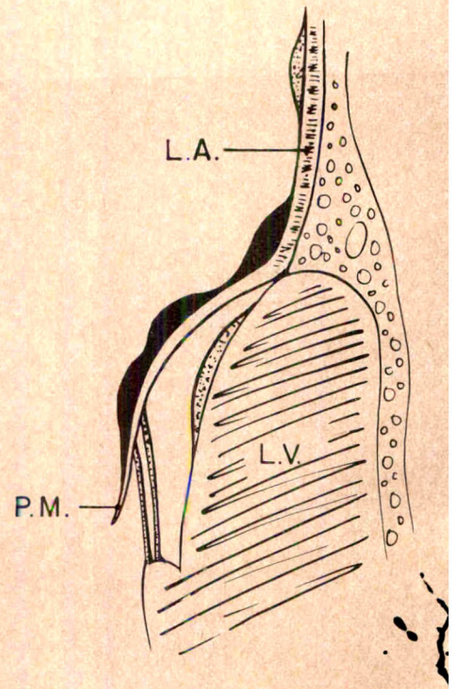

FIGURE 8 (right). Diagrammatic portrayal of sites of fibrosis in relation to mitral valve. **Black areas** indicate areas of most common and heaviest fibrosis. **Lighter shaded areas** of chordae, atrial wall and subvalvular left ventricular endocardium are less commonly involved. L.A. = left atrium; L.V. = left ventricle; P.M. = posterior mitral leaflet.

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Caseating Granulomas of the Heart

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A 49 year old woman died suddenly having had known rheumatic mitral valve disease and severe rheumatoid arthritis for many years. Several calcified masses within her myocardium proved on autopsy to be caseating granulomas almost certainly due to tuberculosis.

Tuberculosis of the heart is rare and to judge from published reports, it is becoming even less frequent. Because of increasingly better control of tuberculosis, this is to be expected. In 1939, Custer and Charr[1] reviewed 14,493 deaths due to tuberculosis and found 64 cases of tuberculosis of the heart. Norris,[2] in 1904, observed 6 cases of tuberculosis of the heart in 1,764 patients who died of tuberculosis. In Poland it was recently reported[3] that one case of cardiac "caseous tumor" was found in 20,000 autopsies.

Pathologically, three types of tuberculosis of the heart are fairly well distinguishable: (1) miliary tuberculosis, in which the heart is among the organs involved; (2) diffuse infiltrating interstitial disease; and (3) caseating nodular disease (tuberculoma). Miliary tuberculosis of the heart is by far the most frequent; tuberculomas are much rarer. The heart may contain one or more tuberculomas.[4–6] The lesions may involve the atria, the ventricles or the ventricular septum,[7] and may extend from a pericardial focus. Tuberculomas may lead to heart block[8] or other abnormal rhythms,[9] and have been reported to lead to myocardial rupture[10] or right ventricular outflow tract obstruction.[11] In this report we present a case of caseating granuloma of the heart.

Case Report

The patient, a white woman, died in July 1972 at age 49 years. She had been followed up by the author from age 12 years. At age 10 (1934) she had scarlet fever, followed by a persisting illness with albuminuria and evidence of acute nephritis. In 1936, a diagnosis of subacute glomerulonephritis and rheumatic fever with mitral valve disease was made. Systolic and diastolic murmurs were heard in the mitral area. Her condition improved after bed rest, but evidence of mitral stenosis and insufficiency remained and the left atrium was noted to be enlarged in 1940.

In December 1942, she married and subsequently had a normal pregnancy and was delivered of a son in December 1943. in 1946 she had a bothersome cough accompanied by a low grade fever. Chest X-ray films were normal, blood cultures were negative as were studies for lupus erythematosus. A specific diagnosis was never made, although her problem was thought to be a persisting bronchial infection after repeated upper respiratory infections.

In 1950 her thyroid became enlarged and classic symptoms of thyrotoxicosis developed. After a partial thyroidectomy in 1951, her condition improved.

In 1953 arthritis developed and progressed to severe crippling rheumatoid disease. This appeared to be related to a respiratory infection with bronchitis. Despite the rheumatic heart disease and rheumatoid arthritis, she had a second pregnancy and was delivered of a boy; there were no complications. In 1956 she had clinical and laboratory evidence of recurrent hyperthyroidism which was alleviated after treatment with propylthiouracil. She continued to

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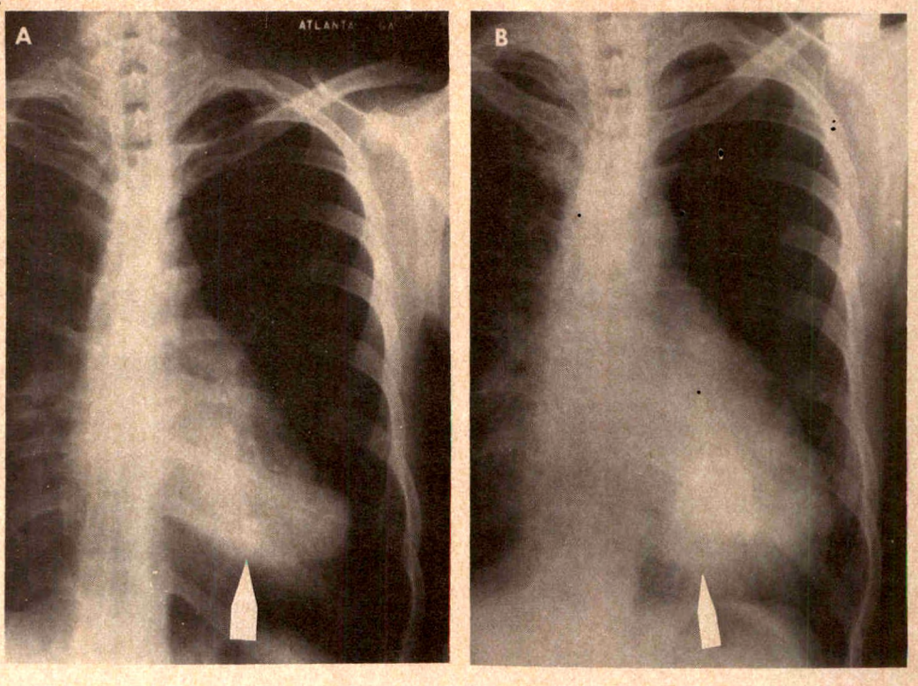

FIGURE 1. Chest roentgenograms showing area of calcification in left ventricle **(arrow). A,** December 30, 1957. **B,** August 10, 1971.

receive small doses of this medication until her death; her serum protein-bound iodine levels remained normal. One year later she was hospitalized because of the severe rheumatoid arthritis and for the first time calcification was noted in the left ventricle near the mitral valve (Fig. 1A). It was assumed to be calcification in the mitral annulus. She received small doses of prednisone over a 30 day period, followed by large doses of salicylates. In retrospect, it was noted that during this period her father underwent bronchoscopic examination and was found to have basal bronchiectasis; a sputum culture was positive for M. tuberculosis. In 1958 the patient was again hospitalized with severe rheumatoid arthritis. Her axillary and epitrochlear lymph glands were enlarged, and she also had rheumatoid nodules on the olecranon. She was referred to a rheumatologist who gave her prednisone therapy for 3 weeks and then began treatment with gold salts which was continued through 1961. The lymph nodes receded in size.

Cardiac catheterization findings: In 1969 it became obvious that the calcium in the heart was not associated with the mitral annulus and that two distinct calcified areas were present. Cardiac catheterization with angiography was performed on August 14, 1969 by Dr. Arnoldo Fiedotin at St. Joseph's Infirmary, Atlanta, Ga. The summary of his report is as follows: "Calcific mass involving the epicardium and myocardium of the lateral aspect of the left ventricle, producing extrinsic total obstruction of the atrioventricular branch of the circumflex, with collateral opacification of the distal atrioventricular branch of intracoronary collateral vessels from both the anterior descending and circumflex coronary artery. Very minimal irregularities of arteriosclerotic nature in the initial aspect of the circum-

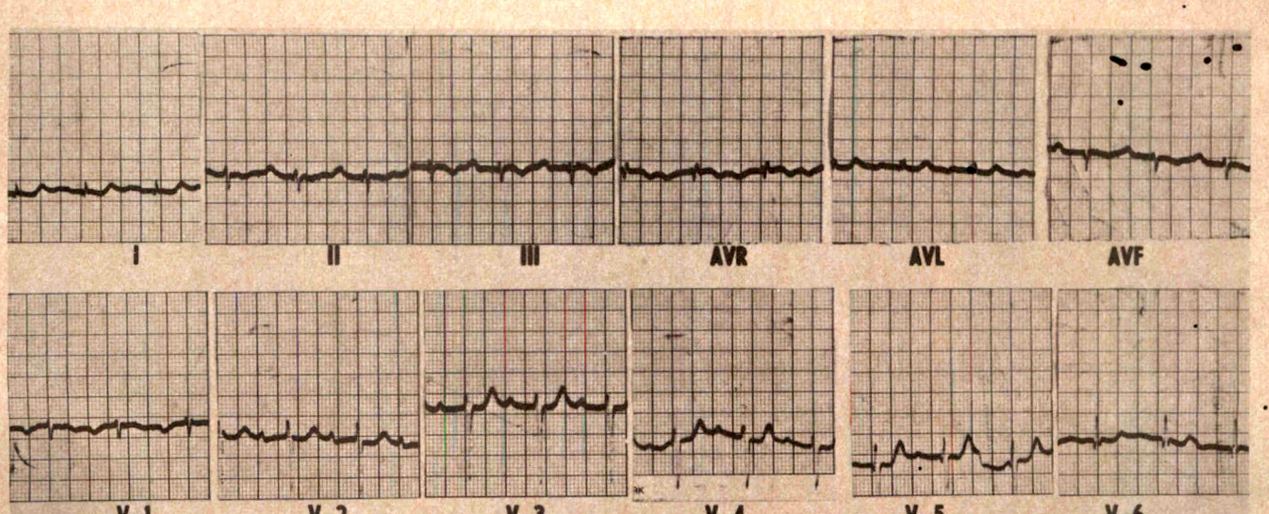

FIGURE 2. Electrocardiogram obtained August 6, 1970 showing a prolonged P–R interval, low voltage of the QRS complex and small R waves in leads III and aVF.

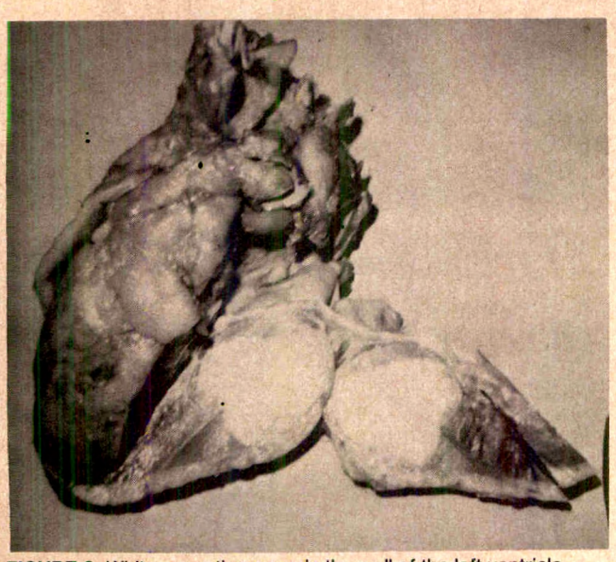

FIGURE 3. White caseating mass in the wall of the left ventricle.

flex coronary artery. Rheumatic heart disease with moderate noncalcific mitral insufficiency and mild mitral stenosis. A second area of calcification is apparent in the anterior pericardium overlying the right ventricular apex and interventricular septum." A chest X-ray film taken on August 10, 1971 (Fig. 1B) showed that the major area of cardiac calcification was larger than in 1969. The patient did quite well despite severe arthritis until her death in 1972 which occurred suddenly, without warning, while she was preparing to eat lunch.

It is interesting to note that the P–R interval in the patient's electrocardiograms became gradually prolonged over a 34 year period. Representative measurements (in seconds) are as follows: 0.16 (1936), 0.20 (1951), 0.22 (1954), 0.24 (until 1962), 0.26 (until 1969) and 0.30 (1970). The electrocardiogram also showed a gradual loss of the R wave in leads III and aVF during this period. (Fig. 2).

Pathologic findings: Autopsy was performed by Dr. John T. Godwin at St. Joseph's Infirmary, Atlanta. The mechanism of death was not determined. The heart weighed 600 g. Moderate mitral stenosis and mitral insufficiency were present. The pericardium was adherent to the lateral surface of the left ventricle beneath which was an area of grayish white pultaceous material measuring 4.2 cm in diameter (Fig. 3). It extended to, but did not involve, the endocardium. The grayish white material was surrounded by dense fibrous tissue (Fig. 4). A smaller but similar area was found in the right ventricular wall. The adherent pericardium contained several smaller caseating nodules. There was also a 0.3 by 0.4 cm nodule in the lower lobe of the right lung. No tuberculosis organisms were seen in, or cultured from, these lesions. The pathologist reported, "Although this lesion has the characteristics of a chronic granuloma such as tuberculosis, one cannot make an absolute diagnosis in view of the absence of positive culture material or lack of organisms in tissue stains."

Discussion

Although no tubercular organisms were demonstrated in either the lungs or the heart of the patient,

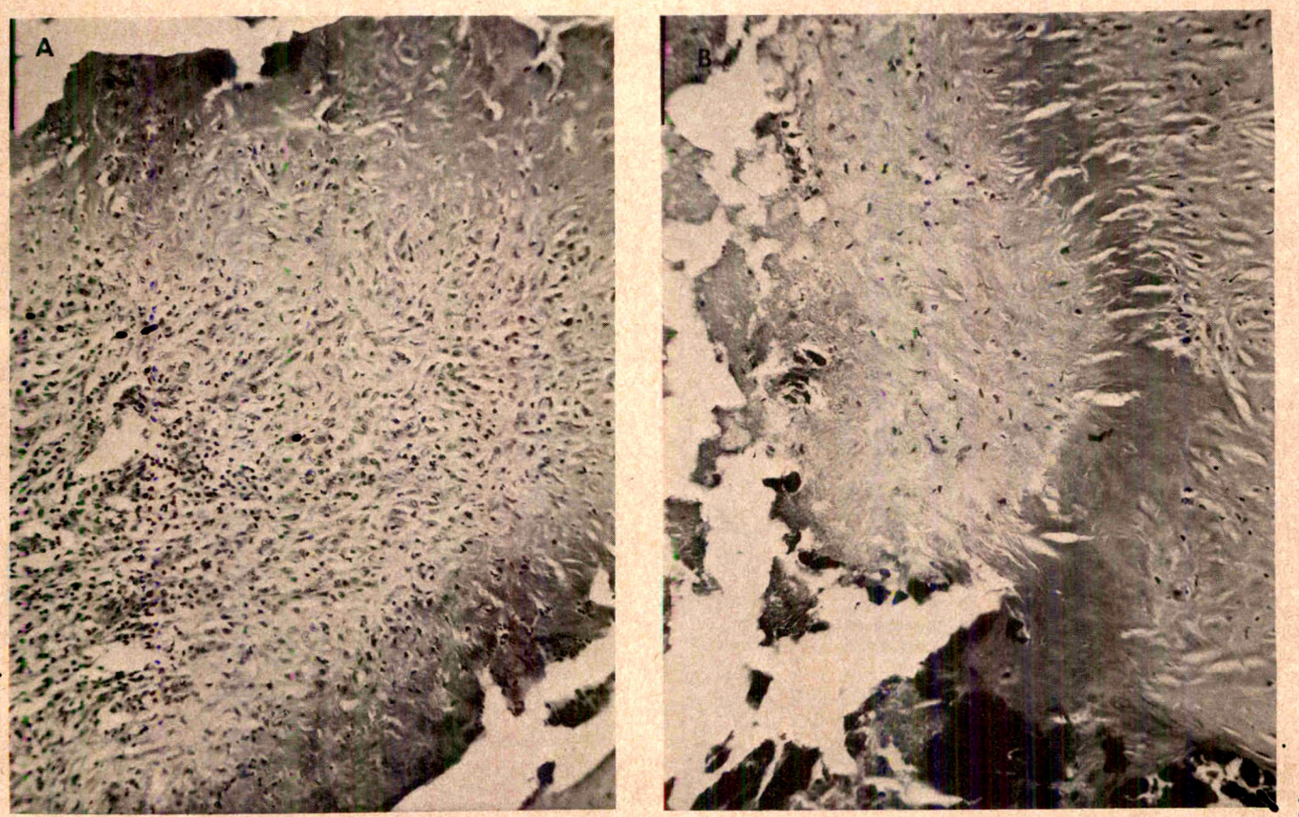

FIGURE 4. Photomicrographs of granulomas. (Hematoxylin-eosin ×200, reduced by 3 percent.)

the granulomas and the smaller nodular caseating areas were typical of tuberculomas. Other types of granulomas seem unlikely in this case. There was no laboratory or clinical evidence of syphilis. The granulomas of rheumatoid disease are much smaller than the myocardial granulomas demonstrated in our case and they do not show extensive caseation. This patient was closely associated with her father who had a bronchial washing positive for tuberculosis. In retrospect a lymph node biopsy in 1958 might have been helpful in making a diagnosis in the case.

The cause of death of the patient is not clear. It occurred suddenly and without premonitory signs to her family close by. She did not have evidence of emboli, congestive heart failure or cerebral hemorrhage at autopsy. We know that there was extrinsic pressure on the circumflex coronary artery by the large granuloma. The electrocardiogram showed the P–R interval increasing in length over a period of 34 years, and R waves were small or absent in leads III and aVF for several years. Although there was no evidence of coronary thrombosis at autopsy, insufficiency of flow may have led to complete heart block or rapid myocardial insufficiency.

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Emergency Thrombectomy for Acute Coronary Bypass Graft Occlusion

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Emergency thrombectomy of occluded aortocoronary saphenous vein bypass grafts was successfully performed in two patients. Thoracotomy and thrombectomy were required in one patient to terminate a fatal arrhythmia. Coronary angiography preceded thrombectomy in another patient who had an acute myocardial infarction postoperatively. Coronary angiography should be performed when signs and symptoms of myocardial ischemia reappear in the immediate postoperative period; if an occluded graft is found, thrombectomy should be performed.

Relief of angina pectoris after coronary bypass grafting is usually prompt and often dramatic. The mortality and morbidity rates associated with this operation are exceedingly low in many centers.[1–3] However, myocardial infarction is a recognized complication of the coronary bypass operation[2]; it may result in inability to terminate cardiopulmonary bypass successfully or cause death from the low cardiac output syndrome within a few hours or days after operation.[2,4] Serious arrhythmias are also seen with myocardial ischemia and can result in death if not promptly treated.[4] The sudden reappearance of myocardial ischemia during the early postoperative period is an uncommon event that suggests malfunction of a graft carrying a critical blood supply to the heart.

This report concerns two patients who had symptomatic occlusion of a bypass graft during early convalescence; both were successfully treated by emergency operative thrombectomy.

Case Reports

Case 1

A 50 year old real estate developer had been incapacitated by severe angina pectoris for 6 months. Coronary arteriography showed 90 percent stenosis of the proximal left anterior descending artery and occlusion of a dominant right main artery. The right posterior descending artery was opacified through collateral vessels from the left coronary arterial injection. At operation, saphenous vein bypass grafts were inserted into the left anterior descending and right posterior descending coronary arteries and intraoperative mean graft flows of 120 and 60 cc/min, respectively, were measured. On the 5th postoperative day unheralded ventricular fibrillation developed. The patient's ventilation was supported and circulation maintained by external cardiac massage. Fifteen separate attempts at defibrillation (400 watt/sec) were unsuccessful despite normal levels of blood pH, PO_2, serum potassium, and a systolic blood pressure of 80 mm Hg. Emergency bedside thoracotomy revealed an occluded right saphenous vein graft. Three additional attempts at internal defibrillation (30 watt/sec) were unsuccessful. While open chest cardiac massage was being performed, thrombectomy of the graft and the posterior descending artery was accomplished using a balloon-tipped catheter introduced through a small incision in the vein. Vigorous pulsations were present in the graft after closure of the venotomy, and the heart was easily defibrillated. The circulation became immediately stable, and the patient

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was moved to the operating room. Upon inspection of the graft, some remaining thrombus was palpated in a cul-de-sac adjacent to a valve near the aortic anastomosis. This portion of the graft was revised without reinstituting cardiopulmonary bypass. After reanastomosis the mean graft flow measured 30 cc/min. The wound was irrigated with saline and antibiotic solution and closed. Ventricular arrhythmias occurred for the next 10 days but were controlled medically. Electrocardiograms did not show evidence of an infarction. Convalescence was prolonged by a wound infection requiring drainage and debridement on several occasions with eventual wound healing. Coronary arteriography 5 months after operation demonstrated a functioning left anterior descending graft and an occluded posterior descending graft. The patient is alive 2 years after operation and has had no recurrence of angina.

Case 2

A 50 year old refrigerator repairman had a diaphragmatic wall myocardial infarction 12 months previously, followed by progressively increasing angina pectoris on exertion. He became unable to work because of chest pain. Coronary arteriograms were obtained which showed an 80 percent stenosis of the left anterior descending artery with retrograde filling of the distal portion of an occluded right coronary artery through collaterals. Coronary bypass grafts were inserted in the left anterior descending and the distal right main coronary arteries. Mean graft flows were 60 and 20 cc/min, respectively. The patient was walking about the ward on the 8th postoperative day when he experienced precordial pain with neck and arm radiation and diaphoresis. His circulation remained stable. Electrocardiograms revealed sinus tachycardia (120 beats/min) and S–T segment elevation in precordial leads V_2 through V_5 that was not present previously. He was moved to the cardiac catheterization laboratory where arteriography demonstrated patency of the right graft but occlusion of the left graft and, in addition, occlusion of the mid-portion of the left anterior descending coronary artery (Fig. 1A). At repeat surgery, within several hours of the onset of the symptoms, the left anterior descending graft was found to be completely thrombosed beginning in the mid-portion at a site where a large side branch of the vein had been ligated leaving a 3 mm stump. Proximally the graft was patent. Under cardiopulmonary bypass the graft was opened and the thrombus extracted from the graft and from the left anterior descending artery using a balloon-tipped catheter, establishing both antegrade and retrograde flow in this vessel. The cul-de-sac containing a large side branch was excised and the graft reanastomosed at this point. The postoperative course was uncomplicated. The electrocardiogram revealed evolution of an anterior-inferior myocardial infarct associated with mild elevation of serum isoenzyme levels which returned to normal within 5 days. Three weeks after reoperation, coronary arteriography showed both grafts to be patent (Fig. 1B). The patient is presently alive and free of angina 9 months after operation.

Discussion

Symptomatic occlusions of aortocoronary bypass grafts are uncommon in the immediate postoperative period and the 2 patients described in this report represent the only instances seen in more than 150 patients operated upon at the Portland Veterans Administration Hospital during the past 3 years. In general, occlusion of a coronary bypass graft is heralded by the onset of recurrent angina pectoris within a few

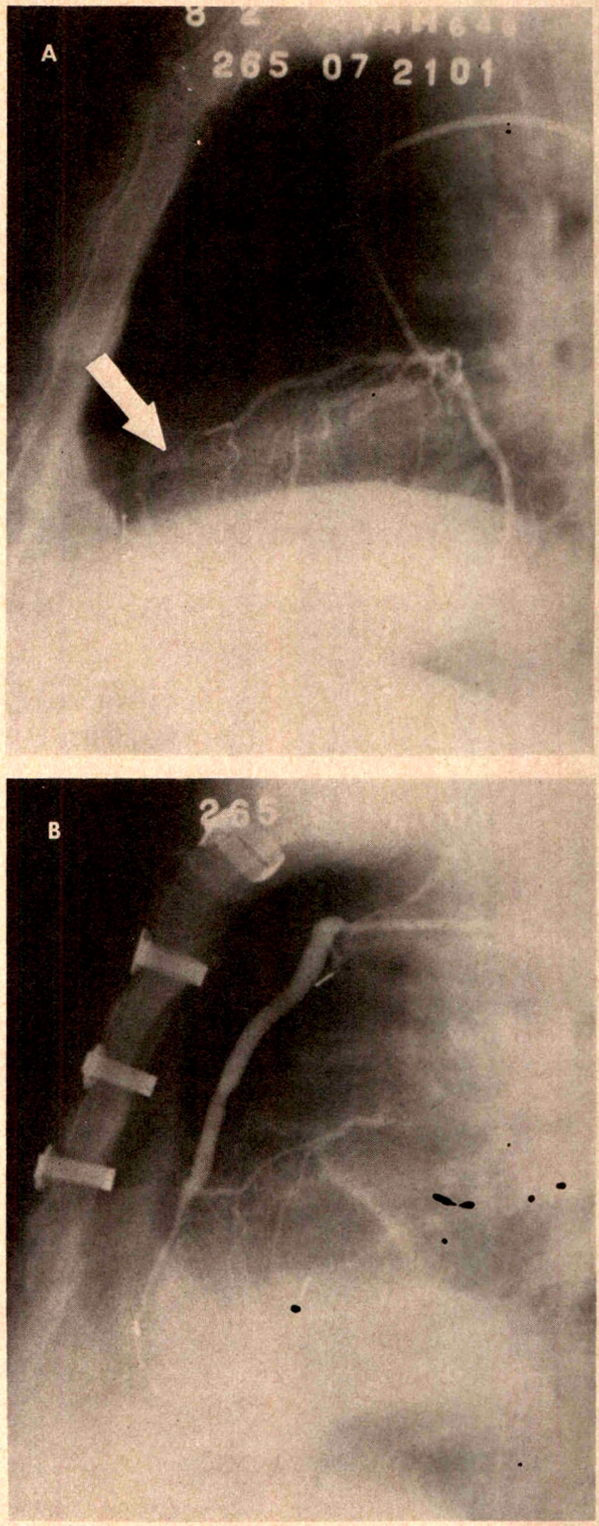

FIGURE 1. Case 2. **A,** left coronary angiogram demonstrating occlusion of the mid-portion of the left anterior descending artery at the anastomotic site **(arrow).** The vein graft was not visualized. At reoperation, thrombus extended from the distal vein graft into the left anterior descending artery. Note the diseased proximal left anterior descending artery. **B,** selective injection of the saphenous vein graft to the left anterior descending artery, 3 weeks after reoperation. The vein graft to the right coronary artery was patent.

months of operation.[1] Serious arrhythmias and myocardial infarction would seem to be more likely when a graft supplying an obstructed coronary artery without much collateral circulation fails[2] or when thrombus from an occluded vein graft extends into the coronary artery and further interrupts blood flow to a portion of the myocardium that is already compromised because of proximal coronary artery disease. This latter situation occurred in both of our patients.

Causes of early graft occlusion: Many factors have been held responsible for early occlusion of coronary bypass grafts including position and redundancy of the graft, its distortion by development of fibrous adhesions, excessive tension on the anastomosis, and injury to the vein graft itself.[5–7] Other factors include poor runoff of the distal coronary bed[8] and discrepancy of size between the saphenous vein and the coronary artery to which it is anastomosed.[9] Technical factors may have been partly responsible for the thrombosis in our patients. Proximity of a venous valve to the aortic anastomosis appeared to be the origin of thrombus in the graft of the first patient. A cul-de-sac created by failure to ligate a large side branch flush with the vein wall was the origin of thrombus in the second patient. In each case a combination of turbulence and stasis of blood as a result of the cul-de-sac was probably the cause of clot formation and eventual propagation.

Treatment of early graft occlusion: Occlusion of a graft in itself may not be a catastrophic or even a clinically recognizable event in a patient after bypass surgery.[10] However, patients who have sudden reappearance of symptoms and signs of myocardial ischemia in the immediate postoperative period should be considered candidates for emergency coronary arteriography to assess the patency of vein grafts and the coronary arteries to which they are anastomosed. If an occlusion can be demonstrated, the patient should be reoperated upon, thrombectomy of both the vein graft and coronary artery performed, and the precipitating cause of the thrombosis corrected. Thrombectomy was necessary in both of our patients and resulted in termination of a fatal arrhythmia in one and cessation of acute ischemia in the other.

Theoretically, technical factors resulting in early occlusion of aortocoronary bypass grafts can be eliminated. However, an awareness of the possibility of early thrombosis of the vein graft must be maintained, and an aggressive approach taken by both the medical and surgical staff to afford patients the opportunity for prolonged survival and a more complete relief of symptoms.

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Right Ventricular Function in Acute Myocardial Infarction

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Right ventricular function has been evaluated by the measurement of right atrial or central venous pressure in many experimental and clinical studies. The assumption that the function of the right and left ventricles was similar led to the use of the central venous pressure as a measure of left ventricular performance.[1] Clinically, central venous pressure has been used to estimate the effective blood volume and the adequacy of ventricular filling in conditions of acute hypovolemia and septic shock. In patients with acute myocardial infarction the central venous or right ventricular end-diastolic pressure may be increased, and this finding has been interpreted as evidence of impaired left ventricular function as well as increased venoconstriction and peripheral vasoconstriction.[2,3] The increase in central venous pressure in myocardial infarction may depend not only on the severity of impairment of the left ventricle, but also on the involvement of the right ventricle.[2,4] The papers by Guiha, Cohn and their colleagues[5,6] recently published in this Journal propose additional considerations in the evaluation of right ventricular function in patients with acute myocardial infarction. Their observations suggest that impaired right ventricular function can result from a right ventricular infarction.

For many years it was considered that the left and right ventricles functioned in parallel fashion and that disparate performance of the two ventricles could not occur without massive pulmonary edema or circulatory collapse. Henderson and Prince[7] demonstrated in the isolated cat heart that increased left atrial pressure would produce a larger ventricular output than increased right atrial pressure. Opdyke et al.[8] recorded simultaneous right and left atrial pressures in animals before and after rapid infusion of saline solution. They concluded that left atrial pressure was consistently greater than right atrial pressure, and that the left ventricle was a less elastic structure than the right ventricle. Additional experimental investigations, studies in chronic heart disease and observations in patients with acute myocardial infarction have demonstrated that right atrial pressure cannot be used to evaluate left ventricular diastolic filling pressure.[9–11]

Separation of the levels of right and left ventricular performance was demonstrated experimentally by Case et al.[4] These investigators reduced left coronary flow and produced a depressed left ventricular function curve while the right ventricular function curve maintained a normal ascending slope. Figure 1 illustrates disparate function of the left and right ventricles in a patient with an acute inferior myocardial infarction. Left ventricular filling pressure was measured as pulmonary arterial end-diastolic pressure and right ventricular filling pressure recorded as right atrial pressure. Low molecular weight dextran was rapidly infused while cardiac output and ventricular filling pressures were measured. The stroke work index for each ventricle was calculated and related to the filling pressure to construct ventricular function curves.[12] The right and left ventricular function curves in this patient confirm the existence of unilateral depression of left ventricular performance with impaired coronary blood flow.[13]

Starr and colleagues[14] were unable to produce increases in venous pressure after extensive damage by cautery to the right ventricle of experimental animals. From their study it was concluded that an isolated right ventricular infarction might not produce augmented central venous pressure. The paper of Guiha et al.[5] provides additional experimental data on right ventricular damage and demonstrates that with volume overloading the ventricular function curve of the right ventricle is significantly lower than that of the left ventricle. Their studies suggest that a stress such as volume overload may be required to demonstrate the depressed function of the damaged right ventricle.

Wartman and Hellerstein[15] in their review of 2,000 consecutive autopsies recorded right ventricular infarction in 22 (13.8 percent) of 164 cases of myocardial infarction. In 4 instances there was isolated right ventricular infarction and in the remaining 18 examinations there was either extension of left ventricular infarction into the right ventricle or a combination of right and left ventricular infarctions. Wade[16] reviewed the pathogenesis of right ventricular infarction in 19 hearts studied post mortem and reported

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that the right coronary artery was occluded in 18 instances. The major anatomic lesion was damage to the posterior wall of the right ventricle. In addition, right ventricular infarction tended to occur in hypertrophied hearts exhibiting ischemic disease. The electrocardiographic changes of right ventricular infarction were usually those of an inferior or posterior wall myocardial infarction, but these changes may not be sufficiently specific to permit an accurate clinical diagnosis of right ventricular infarction.

The mechanism for the low incidence of right ventricular infarction in coronary artery disease was attributed for many years to the thebesian theory advocated by Blumgart et al.[17] This theory maintained that the right ventricle possessed an extensive thebesian system that could provide retrograde flow through the thin right ventricular wall. This hypothesis was eventually discarded, and the mechanism was ascribed to a combination of the reduced metabolic needs of the right ventricle and the effects of decreased pressure on the coronary collateral circulation.

Although increased central venous pressure in patients with inferior myocardial infarction had prompted previous investigators to consider right ventricular infarction, the report by Cohn et al.[6] describes the clinical diagnosis of right ventricular infarction. As reported earlier by these investigators[18] in hemodynamic studies on circulatory shock, massive pulmonary emboli were usually associated with increased pressures in the right heart chambers at a normal left ventricular end-diastolic pressure. However, in their recent paper the presence of inferior wall infarction and the negative results of studies for pulmonary emboli raised the possibility of right ventricular infarction, which was confirmed at autopsy in several patients. Furthermore, the recognition of right ventricular infarction carries clinical significance since the selected form of therapy may be different from that for pulmonary emboli. Blood volume expansion and the reduction of systemic afterload proved beneficial in several of the patients described.

The experimental, pathologic and clinical observations on right ventricular infarction in man suggest that the mechanism is frequently extension of the left ventricular infarction into the free wall of the right ventricle. Figure 2 shows the right and left ventricular function curves of a patient who sustained both anterior and inferior wall myocardial infarctions. After volume expansion with low molecular weight dextran, there was marked depression in the right ventricular function curve associated with a depressed left ventricular function curve and a descending limb. Therefore, in a patient with cardiogenic shock and increased central venous pressure one should consider infarction of the left ventricle

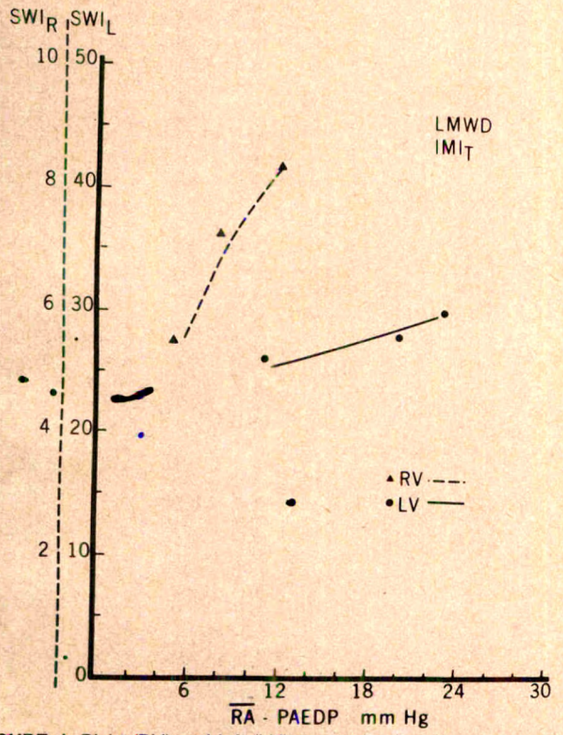

FIGURE 1. Right (RV) and left (LV) ventricular function curves after infusion of low molecular weight dextran (LMWD) in a patient with an acute transmural inferior myocardial infarction (IMI$_T$). The right ventricular function curve demonstrates a normal ascending slope; the depressed left ventricular function curve indicates impaired ventricular performance. PAEDP = pulmonary arterial end-diastolic pressure; $\overline{RA}$ = mean right atrial pressure; SWI$_L$ and SWI$_R$ = stroke work index of the left and right ventricles, respectively.

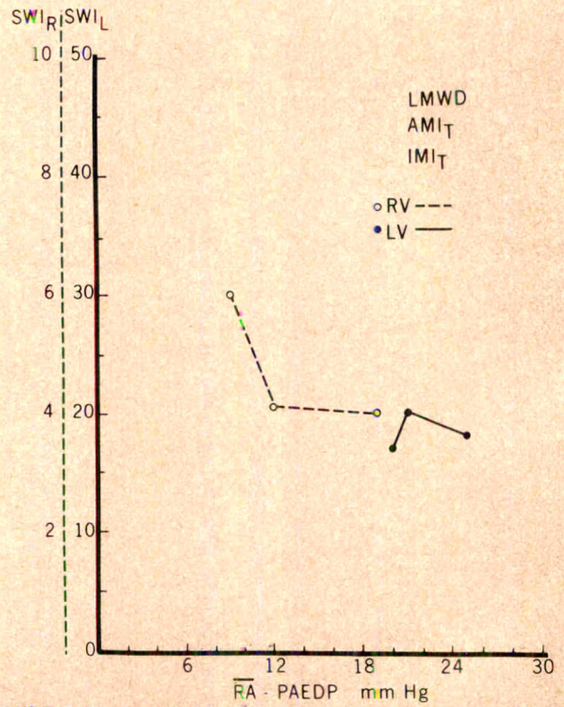

FIGURE 2. Right and left ventricular function curves in a patient with acute transmural anterior (AMI$_T$) and inferior (IMI$_T$) myocardial infarctions during blood volume expansion with low molecular weight dextran. The descending limb of the left ventricular function curve indicates severe impairment of left ventricular performance, and the descending right ventricular function curve suggests extension into the right ventricular wall. Abbreviations as in Figure 1.

with extension into the right ventricle as a diagnostic possibility. Preexisting hypovolemia may mask impaired left ventricular function, which can be further delineated with volume expansion. Under these conditions the left ventricular filling pressure will often increase much more rapidly than right ventricular filling pressure. Usually in massive pulmonary embolism the left ventricular end-diastolic pressure will be normal. Therefore, a depressed left ventricular function curve in the presence of shock and increased central venous pressure should suggest damage to the left as well as the right ventricle.

In summary, analysis of right ventricular function in acute myocardial infarction should consider not only the strain on the right ventricle resulting from left ventricular failure and increased pulmonary arterial pressure, but also the possibility that the left ventricular infarction has extended into the free right ventricular wall. Right ventricular infarction remains clinically and pathologically infrequent, and experimental studies suggest that right ventricular infarction must be an extension from the left ventricle rather than isolated right ventricular damage for depressed function of the right ventricle to occur. A central venous pressure exceeding an abnormally increased left ventricular filling pressure or a depressed right ventricular function associated with a depressed left ventricular function curve should suggest extension of the left ventricular infarction into the right ventricle. Since the clinical evaluation and analysis of the electrocardiogram are not sufficiently sensitive for the diagnosis, right ventricular infarction may be recognized more readily from hemodynamic measurements and assessment of right and left ventricular function. The potentially beneficial therapeutic response to blood volume alterations and vasodilator therapy warrant consideration of right ventricular infarction in this setting as delineated in the papers by Dr. Guiha and associates[5] and Dr. Cohn and co-workers.[6]

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EMERGENCY MYOCARDIAL REVASCULARIZATION

The article by Cheanvechai et al. on emergency myocardial revascularization[1] may be subject to misinterpretation. Two points are worthy of careful examination.

First, the 100 patients "were classified *retrospectively* according to preoperative and serial postoperative enzyme levels." They were classified on the basis of this retrospective classification into two groups as follows: (1) impending myocardial infarction, and (2) acute myocardial infarction. The authors acknowledge the difficulty of making this distinction except retrospectively but fail to recognize the bias introduced when classification is done by hindsight. For example, they state that 6 of the 26 patients with "early phase myocardial infarction" were studied during crescendo angina, and "signs of acute infarction developed during these studies." In addition, the remaining 20 of the 26 had an acute myocardial infarction 3 hours to 7 days after arteriographic studies were performed. It is possible that the arteriographic studies might have contributed to the evolution of a myocardial infarction. Thus, these patients could be considered to have had a complication of angiography. However, with this retrospective classification system, the possibility of a laboratory complication is a logical impossibility.

Second, the authors state that if saphenous vein bypass graft is successful in the group of patients with preinfarction angina, acute myocardial infarction and its sequelae will be averted. Of the 63 patients with impending myocardial infarction who were operated upon, 4 died and 6 had a postoperative myocardial infarction. This is a 15.8 percent complication rate in this group of patients who are supposedly being operated upon to prevent myocardial infarction and its sequelae. No one really knows the true instance of myocardial infarction and death in patients with this syndrome of impending myocardial infarction. At the time I write, there are no published prospective studies dealing with the natural history of this group of patients defined by clinical, electrocardiographic, physiologic and angiographic criteria to compare with data in a similar surgically treated group.

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REPLY

Dr. Conti's letter underscores the difficulties in terminology of acute coronary syndromes and the problems in classifying patients who may be candidates for emergency surgical intervention.

Our classification of patients into the groups of *impending* myocardial infarction or *acute* myocardial infarction was carried out primarily on the basis of symptomatology (intensity and duration of pain, associated hemodynamic sequelae) and electrocardiographic changes that existed at the time of the decision to proceed with the operation. Serum enzyme values were rarely helpful at the time of the decision; therefore, this information was useful only in a retrospective sense. The clinical impression of impending versus acute myocardial infarction was essentially prospective in these patients.

If one hopes to salvage myocardium by early surgical intervention in acute ischemic episodes, it would serve no useful purpose to delay the operation by even a few hours until serum enzyme determinations could be accomplished. The time interval during which myocardium could be salvaged probably varies among patients depending upon several factors including total versus incomplete arterial occlusion, availability and adequacy of collateral protection, and the metabolic requirements of the myocardium.

In the group with impending myocardial infarction, there were six patients who showed evidence of infarction postoperatively and who might well have been included in the acute infarction group by preoperative categorization; however, this was not the clinical impression at the time of surgical intervention in these patients. If one were to add these 6 patients to the infarction group as well as the 4 patients from the "impending" group who died, the infarction group would have consisted of 47 patients with six deaths, a mortality of 12.8 percent, still considerably under that from acute myocardial infarction currently reported from intensive care units in most centers. Postoperative angiographic studies were performed in three of these six patients sustaining postoperative myocardial infarctions. All grafts were patent, and two patients had normal left ventriculograms. The third patient had minimal impairment of the left ventricle. We believe that major myocardial damage was prevented by the bypass grafts in this particular group of patients.

It is, of course, possible that infarction may have been related in some way to arteriographic studies carried out 3 hours to 7 days previously; but in only six patients studied during crescendo angina did signs of acute infarction develop *during* the angiographic study. The cause and effect relation between arteriography and subsequent infarction in the remaining 20 patients is speculative. At the time of surgery, none of these patients had signs of mechanical trauma to the coronary arteries.

We agree completely that the assessment of these results is seriously hampered by the lack of a suitable comparison group with similar arteriographic findings and a similar clinical judgment of impending versus acute myocardial infarction at a critical time of decision. Unfortunately, most clinical diagnoses of acute myocardial infarction are also *retrospective.*

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ANALYSIS OF POSTEXTRASYSTOLIC BEATS IN THE DIAGNOSIS OF IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

The degree of left ventricular outflow tract obstruction in idiopathic hypertrophic subaortic stenosis is characteristically variable and depends mainly upon two hemodynamic determinants: the size of the left ventricular cavity and the contractile state of the left ventricular myocardium.[1–3] The analysis of the postextrasystolic beat has been very useful in the diagnosis of this lesion. Because of postextrasystolic augmentation in the force of the left ventricular contraction, obstruction to left ventricular outflow increases after a premature contraction, which results in a paradoxical reduction in the arterial pulse pressure.[4] This sign has been found consistently in idiopathic hypertrophic subaortic stenosis, although occasionally the lesion is manifested only by a lack of the expected postextrasystolic widening of the arterial pulse pressure rather than by its actual decrease.[1] The width of the pulse pressure of the postextrasystolic beat has been found to be the most reliable sign in distinguishing those patients with true idiopathic hypertrophic subaortic stenosis from those who manifest nonobstructive pressure differences due to catheter entrapment at the left ventricular apex.[5]

The obstruction to the left ventricular outflow in idiopathic hypertrophic subaortic stenosis is maximal during the late ejection phase of ventricular contraction because of the progressive apposition of the hypertrophic septal musculature and the anterior leaflet of the mitral valve as the left ventricular cavity decreases in size. This phenomenon explains the typical arterial pulse contour seen in this condition, which consists of a percussion wave of rapid upstroke, followed by a delayed and decreased tidal wave.[6,7] It would be reasonable to expect that an increase in the degree of obstruction occurring during the postextrasystolic beat would be likely to affect mostly the tidal wave portion of the arterial pulse—not necessarily affecting the percussion wave—and thus the diagnosis of idiopathic hypertrophic subaortic stenosis may be overlooked if the percussion wave alone is analyzed.

We recently studied two patients believed to have idiopathic hypertrophic subaortic stenosis on the basis of typical echocardiograms[8] and the presence of a variable outflow gradient at rest that increased with the Valsalva maneuver and isoproterenol infusion; in both cases the diagnosis was confirmed by left ventriculographic findings, but the central aortic pulse tracings failed to show a narrowing of the pulse pressure in the postextrasystolic beat (Fig. 1). On further analysis it was evident that, although the percussion wave pressure of the postextrasystolic beat was considerably wider than that of the control beat, the tidal wave was markedly smaller; this phenomenon coincided with a significant increase in left ventricular pressure and the development of a large outflow tract gradient in late systole. It seems apparent that in the presence of relatively mild obstruction, the vigorous early systolic ventricular impulse that follows a premature beat is transmitted largely unimpeded to the aorta, to be suddenly curtailed later in systole

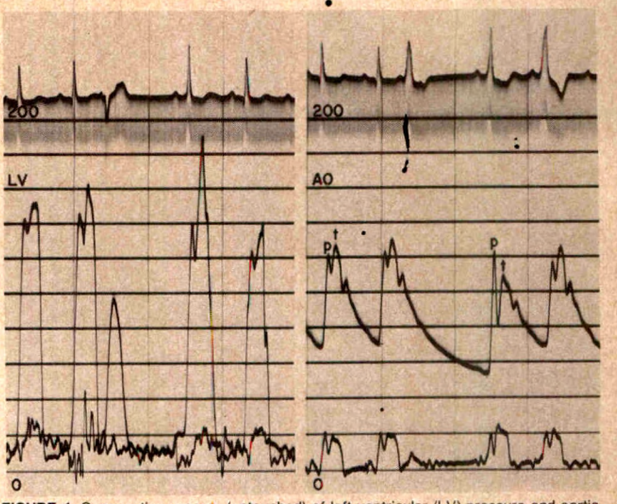

FIGURE 1. Consecutive records (untouched) of left ventricular (LV) pressure and aortic (AO) pressure in a patient with idiopathic hypertrophic subaortic stenosis. After a premature ventricular beat, the left ventricular pressure increases because of an increase in outflow obstruction. The aortic percussion wave (p) of the postextrasystolic beat is wider than that of the control beat, but the tidal wave (t) is markedly decreased. The pulmonary arterial pressure tracing is shown at bottom.

by the development of outflow narrowing as the ventricle continues to eject, and thus a decrease in the arterial tidal wave occurs.

We conclude that in the analysis of the postextrasystolic beat the components of the arterial pulse merit individual consideration and an isolated decrease in the tidal wave after a premature beat is a valid indication of the presence of idiopathic hypertrophic subaortic stenosis even if the overall pulse pressure of the postextrasystolic beat is widened as the result of an increased percussion wave.

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BOOK REVIEWS

CARDIAC ARRHYTHMIAS. TWENTY-FIFTH HAHNEMANN SYMPOSIUM, edited by Leonard S. Dreifus and William Likoff. New York, Grune & Stratton, 1973, 650 pages, $29.75

Only in the past decade has the development of new techniques begun to open the door to the mysteries surrounding many arrhythmias. This volume, consisting of 650 pages and 49 articles, admirably covers the numerous recent advances in both the electrophysiology of the arrhythmias and the clinical application of these findings to diagnosis and treatment.

The symposium fulfills its purpose and does not attempt to be a complete textbook; for example, the basic diagnostic features of each arrhythmia are not presented and there is no specific chapter on arrhythmias in myocardial infarction, His bundle electrocardiography or "sick sinus syndrome." These latter subjects are discussed in one or more articles, and the arrangement of the material in sections, the detailed table of contents and the adequate bibliography facilitate the location of any topic.

The book is divided into seven sections with some overlapping, and, inevitably, some duplication. The longest and most detailed section covers the pathophysiology of impulse formation and conduction. There are comprehensive sections on Wolff-Parkinson-White syndrome, atrioventricular conduction, subjunctional conduction and pacemakers. Individual articles, which can be highly recommended, discuss the combined actions of antiarrhythmic drugs, recognition of premature systoles arising in the Purkinje system and the treatment of intractable arrhythmias.

This volume offers authoritative and well presented material in a field in which basic knowledge and therapy are often limited and tentative. Various theories and points of view are offered and, although this approach sometimes requires detailed reading, the results will be rewarding to the cardiologist.

Harry Jaffe, MD
New York, N. Y.

CIRCULATORY PHYSIOLOGY: CARDIAC OUTPUT AND ITS REGULATION, second edition, by A.C. Guyton, MD, C.E. Jones, MD, T.G. Coleman, PhD. Philadelphia, WB Saunders, 1973, 556 pages

The second edition of this book maintains the tradition of excellence established by the earlier edition. The authors have written a text that is clear and relevant to many of the issues facing physicians in their clinical practice. Important research advances of the past decade are outlined with references readily available. The background of and techniques of testing methods for obtaining cardiac output are detailed in an expanded and scholarly section.

A major contribution appearing in this edition is a two chapter section dealing with qualitative application of computer analysis. The reader is slowly led through what, at first glance, appears to be an electronic quagmire only to find that he is on the other side and on very firm footing. From this firm base, cardiac output regulation in specific physiologic and pathologic states is discussed.

This volume will undoubtedly be the principal reference source on this subject for physicians. This book gives to the medical student, cardiology resident and practicing cardiologist the basic physiologic understanding needed to handle all cardiac problems.

Bertram J. Newman, MD
New York, N. Y.

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and various other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary in method of education.

The National Committee for Continuing Medical Education in the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

To be arranged individually	**Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.
To be arranged individually	**Cardiology and the Problem Oriented System: A Preceptorship in the Practical Use of the System.** J. Willis Hurst, FACC, director. Emory University School of Medicine, Atlanta, Ga.
SEPT. 9–11	**A Symposium on Cardiovascular Nursing.** Fred D. Ownby, FACC and Leo Schamroth, FACC, co-directors. University of Tennessee at Nashville, Nashville, Tenn.
SEPT. 12–14	**Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director and Yoshio Watanabe, FACC and Edward K. Chung, FACC, co-directors. Marriott Motor Hotel, Philadelphia, Pa.
OCT. 7–9	**Vectorcardiography—An Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton, Scottsdale, Ariz.
OCT. 7–9	**Myocardial Ischemia: A Clinical Frontier.** Suzanne B. Knoebel, FACC and Borys Surawicz, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.
OCT. 11–12	**New Techniques and Concepts in Cardiology: 1. Clinical Uses of Echocardiography II. Treatment of Coronary Artery Disease.** Stephen E. Epstein, FACC, director. The Shoreham Americana Hotel, Washington, D.C.
OCT. 15–17	**Problems in Acute Myocardial Infarction.** William J. Grace, FACC, director and Richard J. Kennedy, FACC and James T. Mazzara, FACC, co-directors. St. Vincent's Hospital and Medical Center, New York, N.Y.
OCT. 31–NOV.2	**Core Curriculum: Phonocardiography and Pulse Recording—Workshop.** Morton E. Tavel, FACC, director. Methodist Hospital Graduate Medical Center, Indianapolis, Ind.
NOV. 4–13	**Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.
NOV. 7–9	**Recent Advances and Current Concepts in Coronary Artery Disease.** Edmund H. Sonnenblick, FACC, director. Sheraton Boston Hotel, Boston, Mass.
DEC. 5–7	**Advances in Heart Disease 1975.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.
DEC. 5–8	**Clinico-Pathologic Correlations in Cardiovascular Disease.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, Va.
DEC. 11	**Colloquia in Cardiology—Number 7: Echocardiography.** Robert W. Oblath, FACC and Ronald Danzig, FACC, directors. Ambassador Hotel, Los Angeles, Calif.
DEC. 13–15	**The Eliot Corday Symposium: Recent Advances in Cardiovascular Disease.** Henry I. Russek, FACC, director. New York Hilton Hotel, New York, N.Y.

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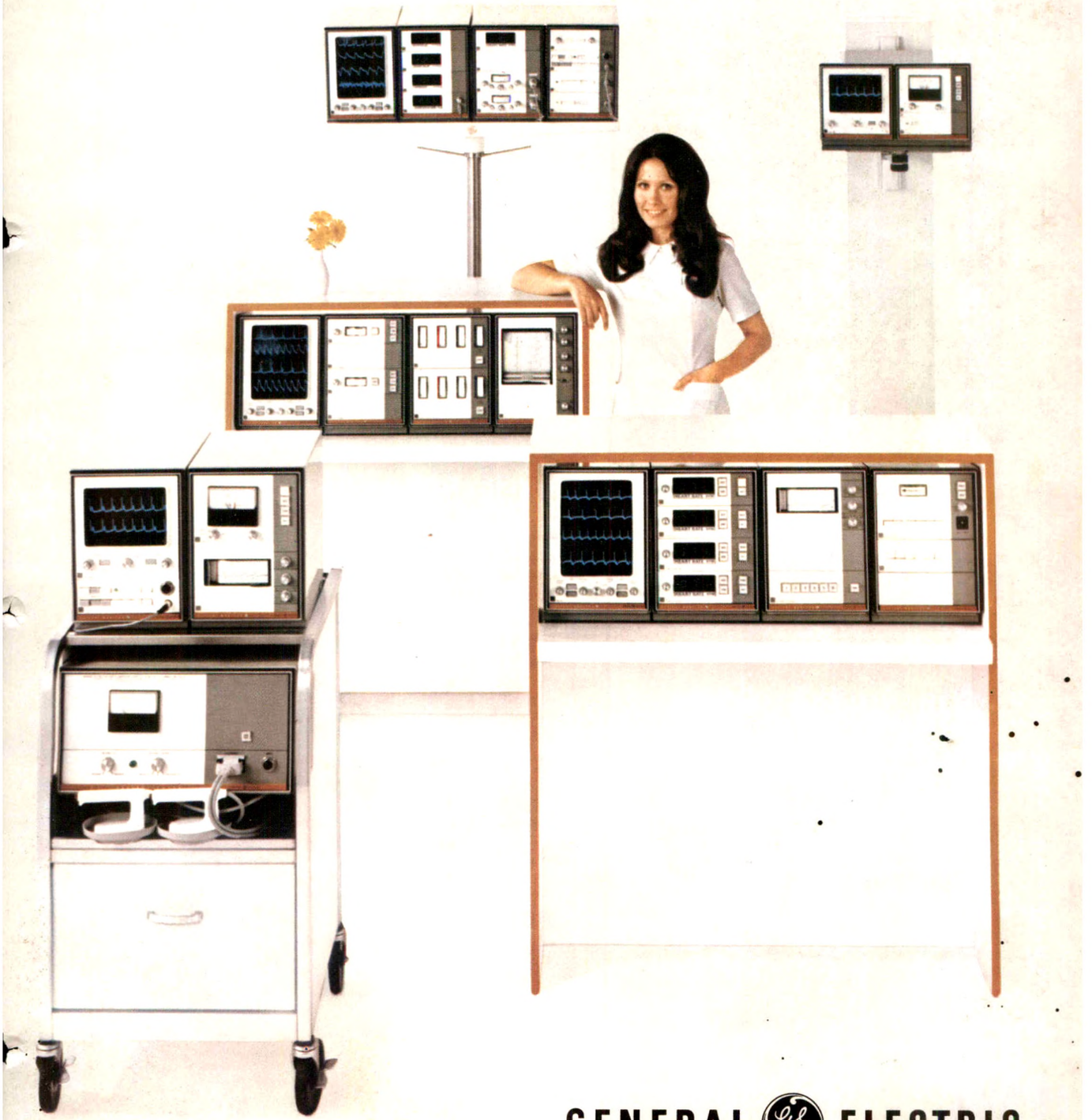

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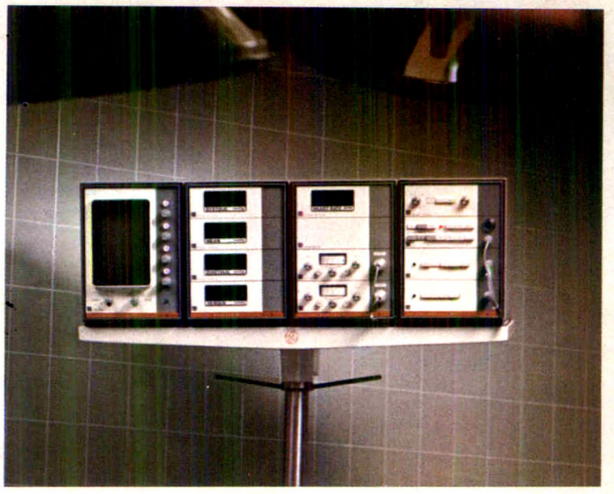

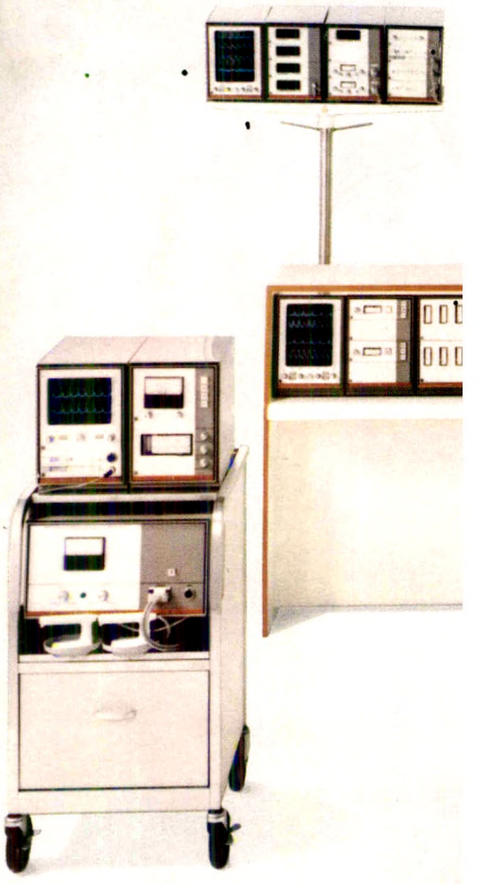

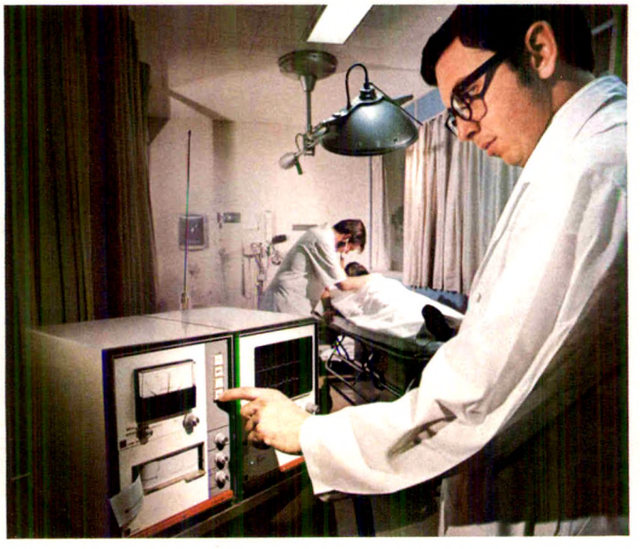

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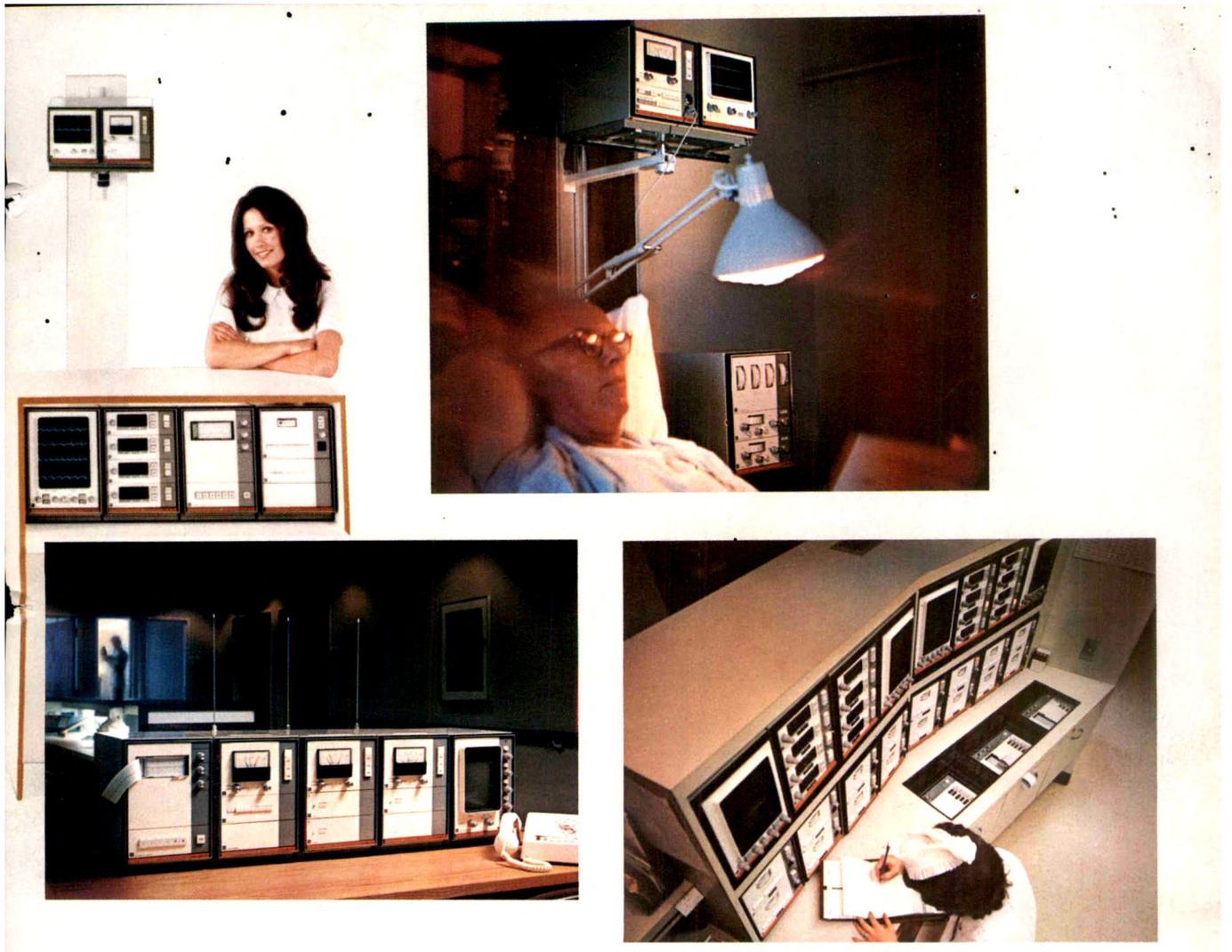

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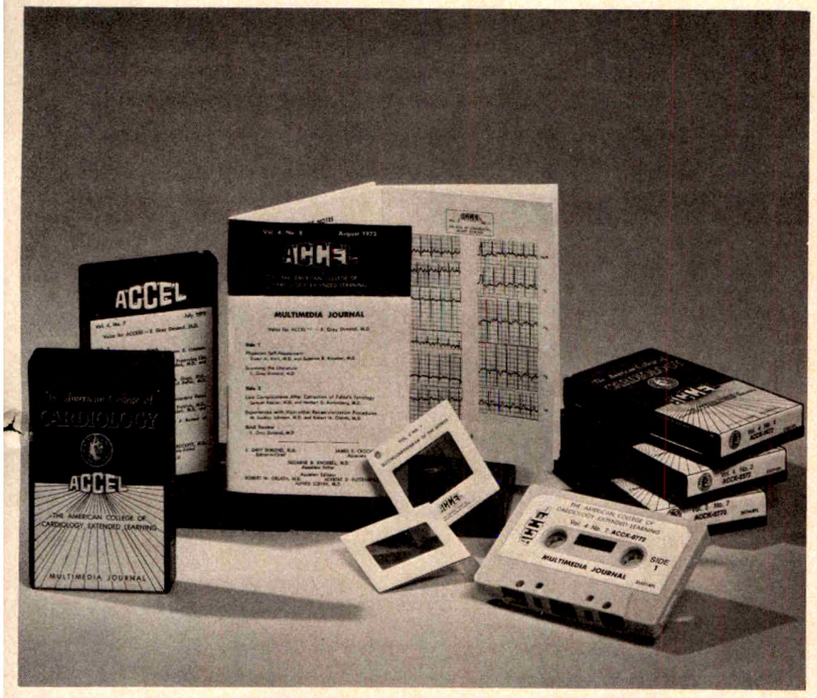

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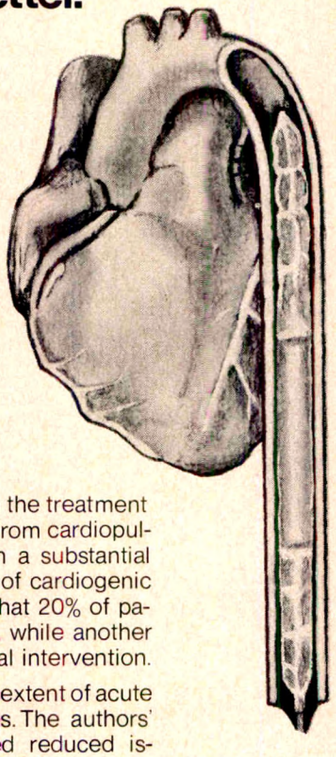

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The IABP's effectiveness is clinically proven in the treatment of cardiogenic shock and in weaning patients from cardiopulmonary bypass. It is a "lifesaving measure in a substantial minority of patients who would otherwise die of cardiogenic shock."[1] Braunwald and Maroko[2] estimate that 20% of patients who would otherwise die can be saved, while another 20% can be stabilized for diagnosis and surgical intervention.

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Hemodynamic criteria to determine if a patient who seems to be going into cardiogenic shock is responding to treatment have been developed by Leinbach.[4] These criteria are a major contribution to the effective application of IABP treatment since *early use* of the system greatly increases the chances of success. Buckley and associates[5] used the IABP in 27 heart-surgery patients who went into shock upon termination of cardiopulmonary bypass. Eighteen survived; 13 are long term survivors. Best results occurred with initiation of IABP therapy early in the postoperative period.

*Developed by Avco Corporation and manufactured for Roche Medical Electronics Division.

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Dunkman and others[6] have concluded that "catecholamines may actually increase ventricular dysfunction and necrosis" whereas the IABP's enhancement of coronary perfusion and reduction of oxygen-consuming work in the left ventricle can save patients if applied before about 40% of the left ventricle is irretrievably damaged. Moreover, IABP permits safe use of drugs if needed.

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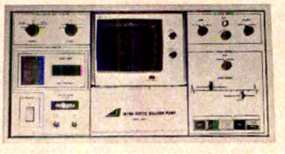

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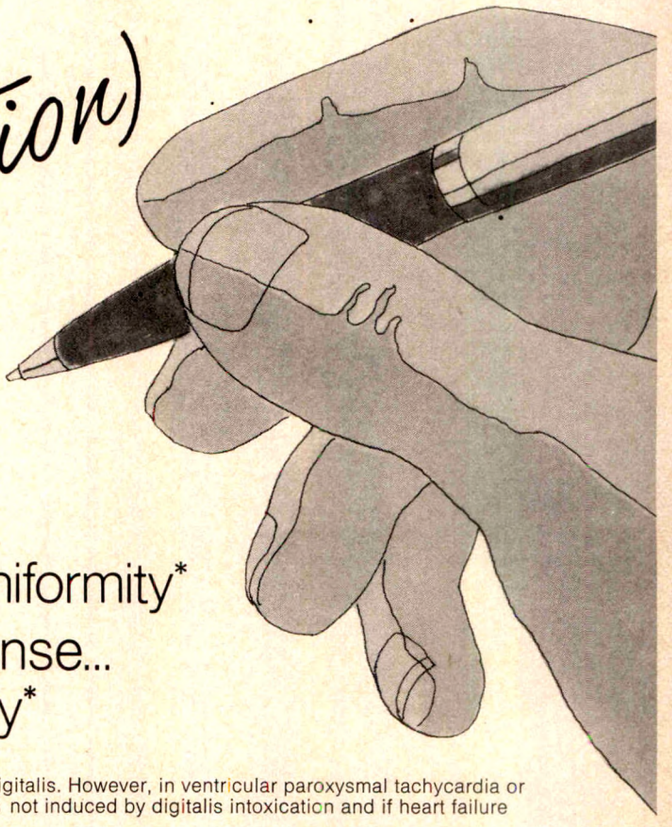

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Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

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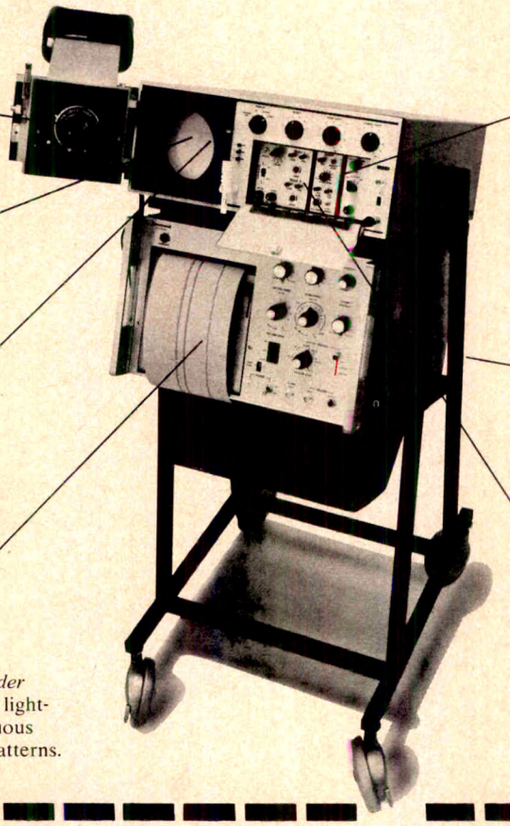

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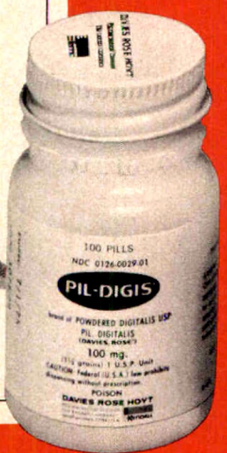

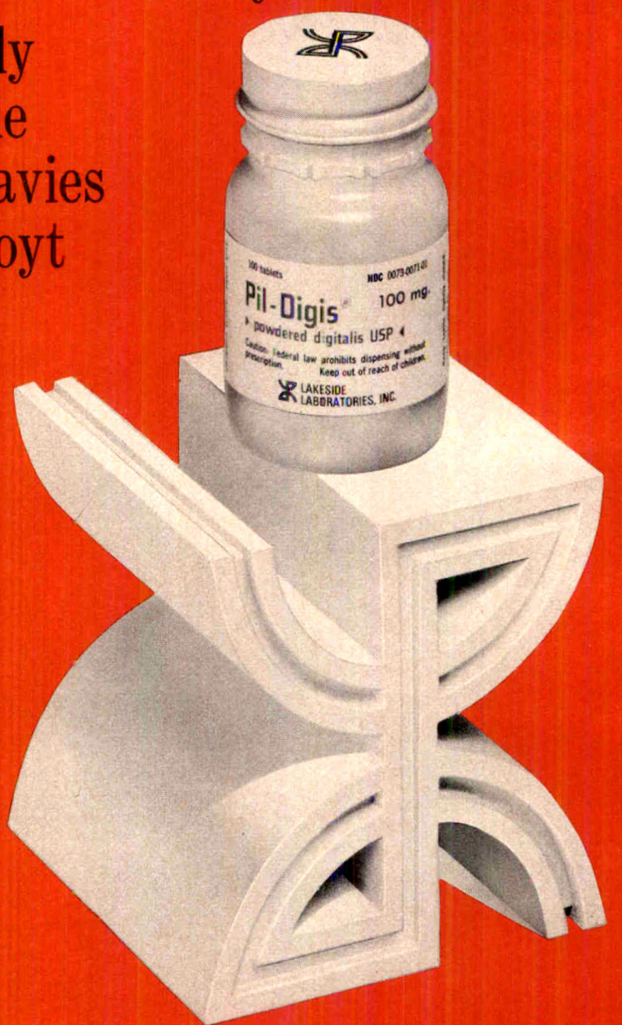

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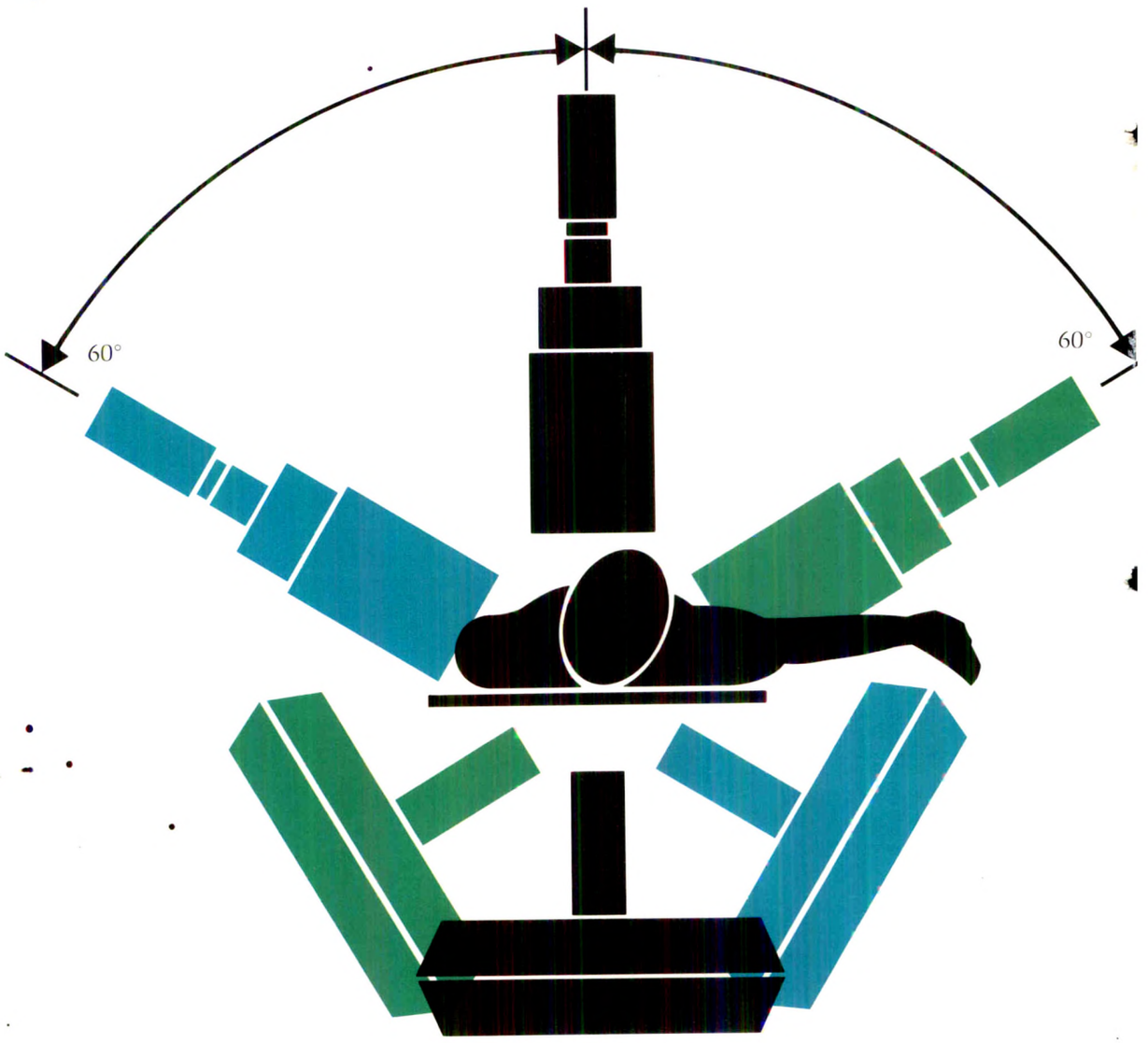

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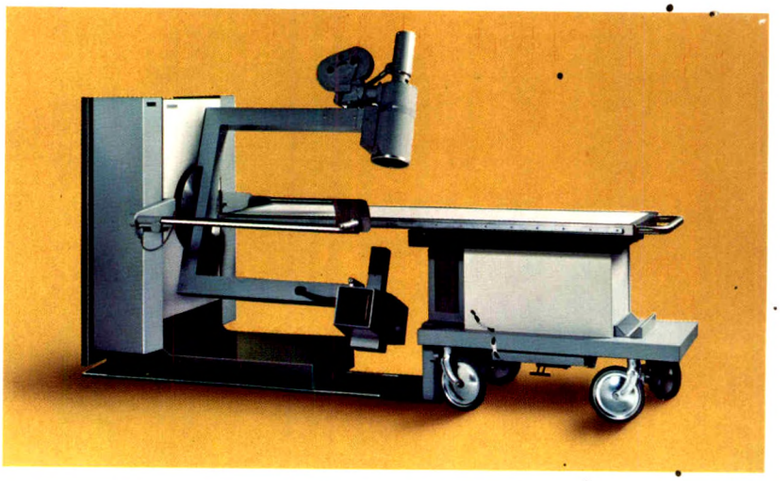

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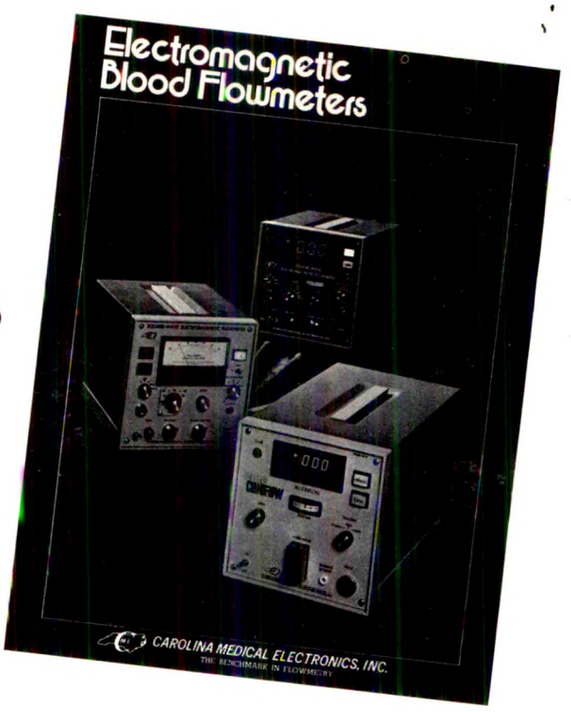

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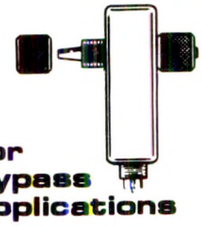

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